The American Journal of CARDIOLOGY

OFFICIAL JOURNAL OF THE *American College of Cardiology*

INDEX ISSUE

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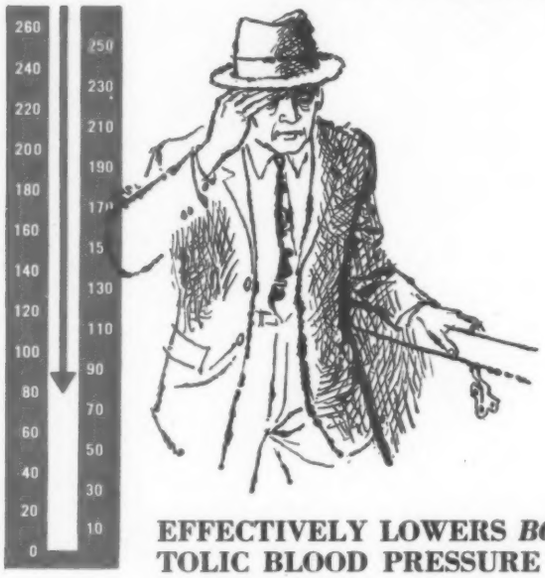
JUNE 1960

New flexible, predictable therapy in essential hypertension



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OSTENSIN produces prompt and prolonged sympathetic blockade. Systolic *and* diastolic blood pressure are smoothly and predictably reduced.

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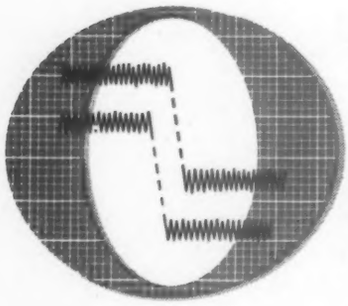
Concomitant use of the newer oral diuretics such as chlorothiazide and its derivatives[1,2] allows reduction in dosage, flexibility in regimen.

FEWER, MILDER BY-EFFECTS

Virtual absence of constipation.[3] Certain other by-effects common to most ganglionic blocking agents occur less frequently and are less pronounced.[1,3,4,5]

TABLETS



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References: 1. Smirk, F.H.: Am. Heart J. *58*:701 (Nov.) 1959. 2. Janney, J.G., Jr., et al.: Am. J. Cardiology *4*:745 (Dec.) 1959. 3. Dunsmore, R.A., et al.: Am. J.M. Sc. *236*:483 (Oct.) 1958. 4. Blaquier, P., et al.: Univ. Michigan M. Bull. *24*:409 (Oct.) 1958. 5. Borhani, N.O.: Ann. Int. Med. *51*:983 (Nov.) 1959.

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The accompanying graph shows a dramatic but by no means unusual instance of the effect of Aldactone in refractory edema.

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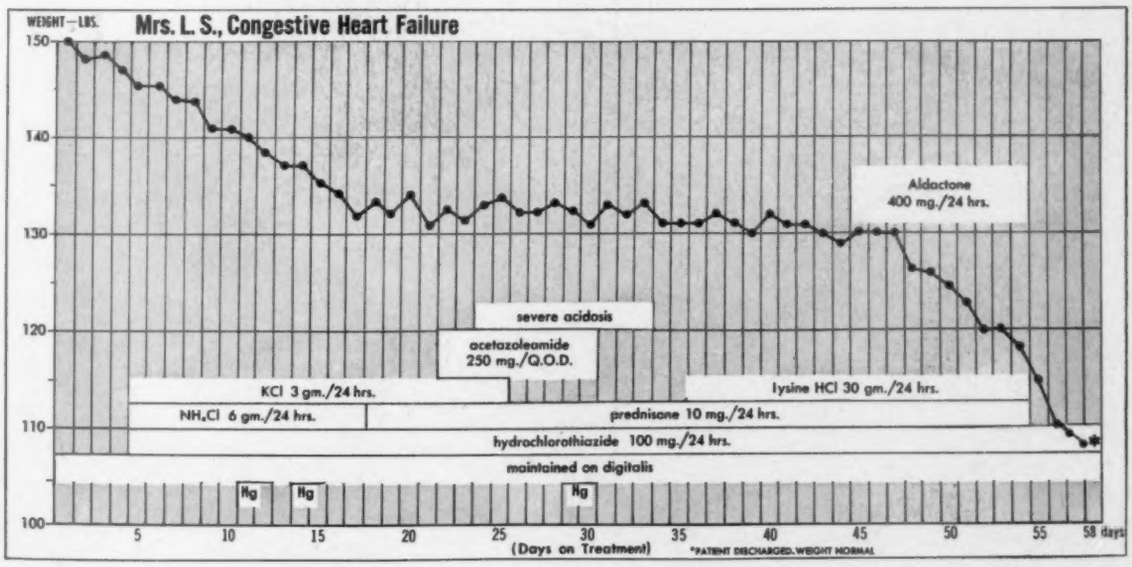

NOW... A DRUG THAT LOWERS CHOLESTEROL LEVELS AS MUCH AS 200 mg.%

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new

NICALEX*

TABLETS aluminum nicotinate, Walker

New NICALEX reduces blood cholesterol levels as much as 200 mg. % with virtually no flushing, itching or g. i. disturbance in over 80% of patients.[1-4] Significant reductions have been obtained in close to 90% of hypercholesteremic patients to date.[1-4] Lowered cholesterol levels can be maintained indefinitely with little or no discomfort to most patients. And there is no need to restrict the diet throughout therapy.

A newly discovered salt of nicotinic acid, NICALEX is "...as effective in reducing blood cholesterol as plain nicotinic acid...."[5] But unlike the older therapy, which produces vasomotor and gastrointestinal side effects in the vast majority of patients, NICALEX is characterized by a markedly reduced incidence of unpleasant reactions.[5]

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Supplied: Bottles of 100 and 1000.

References: **1.** Tandowsky, R. M.: Personal communication. **2.** Parsons, W. B.: In press. **3.** Thompson, C. E.: Personal communication. **4.** Biben, L. H.; Kurstin, W., and Protas, M.: Personal communication. **5.** Hobbs, T. G.: Personal communication.

*PAT. PENDING

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THE AMERICAN JOURNAL OF CARDIOLOGY is published monthly by The American Journal of Cardiology, Inc., Executive and Editorial Offices, 11 East 36th Street, New York 16, N. Y. June 1960, Volume 5, No. 6. Publication office, Easton, Pa. Second-class postage paid at Easton, Pa. Official Journal of the American College of Cardiology.

SUBSCRIPTIONS: United States $12.00 a year; Canada $13.00; Foreign $15.00
SINGLE COPIES: Regular Issues $2.00; Symposium and Special Issues $4.00

MAIL CHANGES OF ADDRESS AND SUBSCRIPTION ORDERS TO: The American Journal of Cardiology, 11 East 36th Street, New York 16, N. Y. Change of address must reach us one month in advance.

MANUSCRIPTS: All manuscripts should be typewritten double space and submitted in duplicate to the Editorial Office of The American Journal of Cardiology, 11 East 36th Street, New York 16, N. Y. The top should be indicated on the back of each photograph. Reference style: Smith, J. S. Treatment of cardiac failure. Am. J. Cardiol. 3: 274, 1959.

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Pentritol Tempules given every 12 hours reduced or eliminated nitroglycerin requirements, stopped anginal attacks or reduced their frequency, eliminated or mitigated pain, and increased the capacity for physical activity. *Patients previously taking PETN in tablets with little progress, responded favorably to Pentritol Tempules.*[2]

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1. Biegeleisen, H. I.: Clin. Med. 2:1005, 1955. 2. Roberts, J. T.: Clin. Med. 4:1375, 1957.

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The American Journal of Cardiology

Volume V JUNE 1960 Number 6

CONTENTS

Editorial

Clinical Studies

The authors present a detailed analysis of direct and indirect aortic and carotid pulse curves in aortic stenosis and mitral stenosis. The ability of the indirect carotid pulse curve to demonstrate significant prolongation of left ventricular ejection in aortic stenosis and somewhat shorter ejection in mitral stenosis has been reconfirmed. Of interest is the description of what may be a characteristic abnormality in the carotid pulse tracing of patients with subaortic stenosis.

Clinical assessment of the severity of pulmonic stenosis can be made fairly accurately from the clinical, auscultatory, phonocardiographic, electrocardiographic, vectorcardiographic and x-ray findings. Severe cases in which right ventricular systolic pressures are over 100 mg. Hg are characterized by effort incapacity, a late peak in the systolic murmur, absent or delayed pulmonary closure, audible auricular sound, pulmonary P waves and marked posterior deviation of the T loop in the horizontal plane accompanying right ventricular hypertrophy.

Six per cent of 445 patients with arterial hypertension had a basal diastolic murmur due to aortic valve insufficiency. An improved phonocardiographic method for recording the medium high frequency vibrations of low amplitude is presented.

Observations in Peru correlate a greater incidence of patent ductus arteriosus with high altitudes presumably due to mechanical factors affecting the pulmonary circulation and a lower oxygen tension. No similar correlation occurred in patients with coarctation of the aorta.

In patients with congestive heart failure and a powerful atrial contraction a double sound may be audible in the femoral region. The first sound, due to atrial systole, is transmitted by the venae cavae to the femoral veins. The second sound, due to left ventricular systole, is transmitted by the aorta to the femoral arteries.

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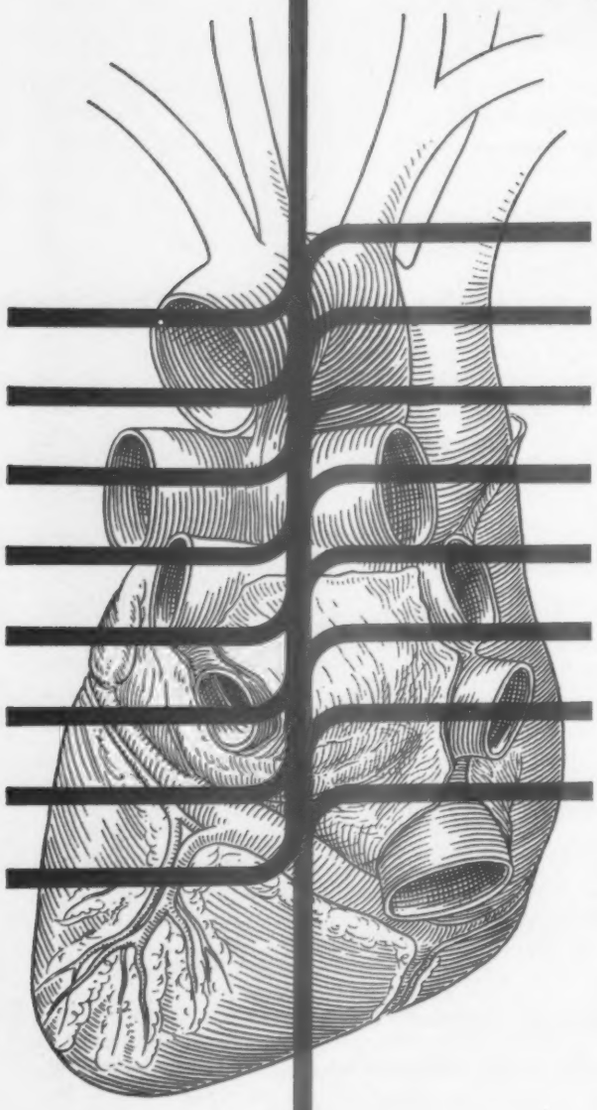
new approach to the concept of "total management" in angina pectoris

new Marplan

a happy balance of potency/safety



Marplan prevents or reduces anginal pain: Marplan is indicated primarily for patients with moderately severe to intractable angina pectoris. It has demonstrated a high degree of effectiveness. When used on a continuous dosage schedule, Marplan prevents pain, increases exercise tolerance and reduces nitroglycerin requirements.

Marplan creates a more confident mental climate: Many angina patients display a more cheerful outlook when on Marplan therapy. This mental improvement is undoubtedly due to the antidepressive action of Marplan. However, it should be stressed that Marplan is indicated for *symptomatic* control of angina pectoris. While it abolishes anginal pain (some patients may achieve a virtually pain-free state), Marplan does not appear to influence the EKG. Hence, as with previously available prophylactic agents, it is imperative that patients be instructed to maintain the same restriction of activity in force prior to Marplan therapy.

Marplan strikes a happy balance of potency/safety: Marplan has been shown to be considerably more potent than certain other amine oxidase regulators. While clinically such increase in potency may be associated with increased side effects, Marplan strikes a happy balance of potency/safety. Marplan has shown markedly fewer of certain of the side reactions of the hydrazines and, moreover, in thousands of cases, there have been no reports of hepatitis attributable to Marplan. Nevertheless, all precautions set forth in the product literature should be strictly observed. Since the precise manner in which Marplan improves the cardiac status is as yet undefined, and since so many patients attain a virtually pain-free state, it is imperative that patients be instructed to maintain the same restrictions of activity in force prior to Marplan therapy.

Complete dosage information, available on request, should be consulted before prescribing Marplan.

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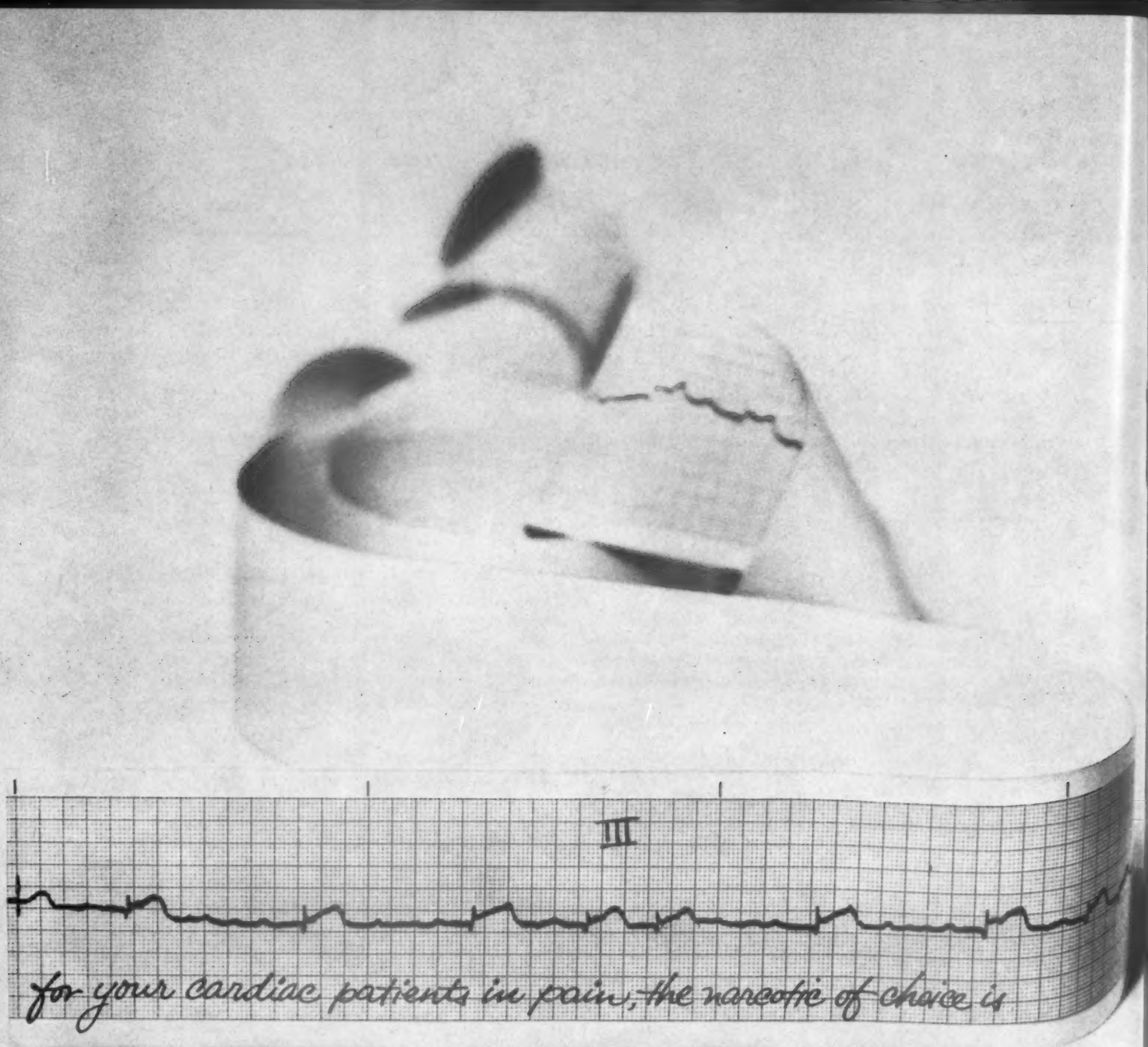

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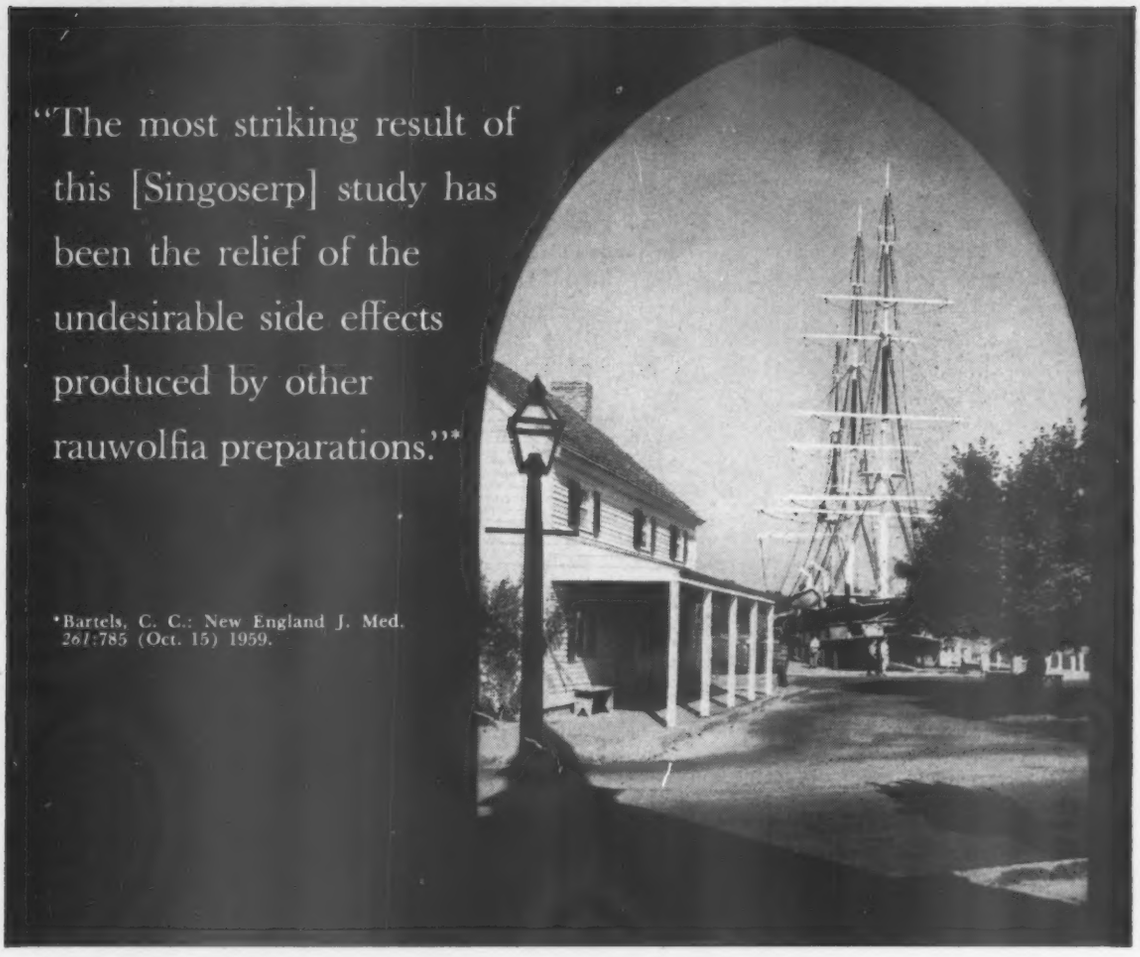
from the New England Journal of Medicine:



results you can confirm in your practice:

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Side Effects	Incidence with Prior Rauwolfia Agent	Incidence with Singoserp
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Lethargy or fatigue	5	0
Nasal congestion	7	0
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Conjunctivitis	1	0

(Adapted from Bartels*)

many hypertensive patients prefer

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because it lowers their blood pressure without rauwolfia side effects

Tablets, 1 mg. (white, scored); bottles of 100.

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Diagnostic Shelf

Special Departments

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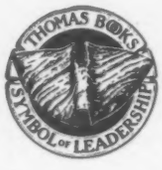
4 BOOKS FOR CARDIOLOGISTS PUBLISHED IN MAY

THE CLINICAL USE OF ALDOSTERONE ANTAGONISTS *compiled and edited by* **Frederic C. Bartter.** Twenty-three experienced investigators survey the clinical and metabolic results of controlled clinical investigation with aldosterone antagonists in man. This symposium is a report of the proceedings of a conference under the Chairmanship of Irwin C. Winter, M.D. **Coverage includes** 1) the fundamental mechanism of action and clinical results with aldosterone antagonists used as a diagnostic tool 2) the use of aldosterone antagonists in patients with cirrhosis and ascites—advantages, limitations, and contraindications for therapy 3) early experiences with aldosterone antagonists in patients with cardiac failure and edema and 4) preliminary studies with the use of aldosterone antagonists in hypertension, nephrosis, and idiopathic edema.

THE CHEMISTRY OF LIPIDS IN HEALTH AND DISEASE: A review of our present knowledge of lipids; their chemical structure, their breakdown and synthesis in living organisms; their place in human nutrition; and their abnormalities of metabolism in disease *by* **H. K. King,** *University of Liverpool.* This is a straightforward, clear summary which integrates the findings of workers over a wide and expanding field. As an elementary exposition of discoveries of the past decade, it conveys the spirit of the **new ideas** rather than becoming just a mere guide-book to literature or an attempt to revise older theories. **Treated in broad outline** are those aspects of chemical structure and physical behavior which are essential for an understanding of lipid chemistry. It surveys the important **new knowledge** concerning digestion, absorption, and metabolic breakdown of lipids. 120 *pp.*, 2 *il.*, (*Amer. Lec. Living Chemistry edited by I. Newton Kugelmass*), $3.75



ELECTRON MICROSCOPY OF THE CARDIOVASCULAR SYSTEM: An Electron Microscopic Study with Applications to Physiology *by* **Bruno Kisch,** *Yeshiva University. Translated from the original German text by* **Arnold I. Kisch. PURPOSE:** To acquaint the medical profession at large and particularly the cardiologist with the important contributions that electron microscopy has made to our understanding of the ultra microscopic structure and function of the cardiovascular system. The author's discovery of the function and the vast quantity of enzyme bearing organisms (sarcosomes) within each muscle fiber of the heart opens new vistas for understanding the function of heart muscle. Also of vital interest are the author's concept of protocapillaries and his studies on the nerves in the heart and its capillaries, and his conclusions concerning the mechanics of angina pectoris, of axon reflexes and of the ultra microscopic structure of nerve fibers.

THE SURGICAL TREATMENT OF PORTAL HYPERTENSION, BLEEDING ESOPHAGEAL VARICES AND ASCITES *by* **M. Judson Mackby,** *Kaiser Foundation Hospital, San Francisco.* To guide the surgeon through the confused tangle of conflicting theories and practices, Dr. Mackby presents what is probably the first complete manual of practical clinical management of the surgical complications of cirrhosis—**A COMPENDIUM OF ALL THAT IS KNOWN, SUSPECTED, OR INFERRED** about this condition. Emphasis throughout is on **exact technique,** including **detailed descriptions** of the various operative procedures currently in use. The PATHOGENESIS is summarized together with PATHOLOGICAL PHYSIOLOGY and some of the important BIOCHEMICAL FEATURES. **Illustrated with 60 outstanding, original drawings prepared for this book only by Artist Laurel Gilliland.** (*Amer. Lec Surgery edited by Michael E. De Bakey and R. Glen Spurling*)

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References: 1. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.

*brand of hydroxyzine

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PUBLISHED CLINICAL RESULTS WITH ACTASE

Source*	Indication	Number of Patients	Results
Moser, K. M., et al.: Circulation 21:337, 1960.	Acute deep thrombophlebitis	62	decreased pain, disability, complications, reduced mortality due to pulmonary embolization—in a controlled study
Singher, H. O., and Chapple, R. V.: Clin. Med. 6:439, 1959.	Pulmonary embolism	33	70% excellent; 24% questionable; 6% poor; "no untoward side effects"
Chapple, R. V., and Singher, H. O.: Canad. M.A.J. 81:231 (Aug. 15) 1959.	Phlebothrombosis	171	65% excellent; 26% good; 9% poor
Howden, G. D.: Canad. M.A.J. 81:382 (Sept. 1) 1959.	Central retinal vein thrombosis	1	"...an excellent thrombolytic response ...remarkable visual improvement"
Carroll, B. J.: Angiology 10:308, 1959.	Phlebothrombosis	82	60 excellent; 19 good; "...a distinct advance in the treatment of thrombophlebitis"
Harloe, J. P.: Angiology 10:283, 1959.	Thrombophlebitis	4	"more rapid resolution...more clear-cut clinical response"
Cliffton, E. E.: Angiology 10:244, 1959.	Peripheral venous thrombosis	38	improvement in large majority
	Pulmonary embolism	5	4 completely relieved
	Retinal vein thrombosis	2	"no further progression"
Moser, K. M.: Angiology 10:319, 1959.	Deep venous thrombosis	41	rapid response if treated within 5 days
Sheffer, A. L., and Israel, H. L.: Angiology 10:292, 1959.	Pulmonary embolism	6	4 excellent; 2 good
	Acute thrombophlebitis	9	good
	Retinal vein thrombosis	7	2 excellent; 5 no benefit
Stewart, C. F.: Angiology 10:299, 1959.	Iliofemoral thrombophlebitis	2	"remarkable" in 1; "considerable improvement" in the other
Evans, J. A., and Smedal, M. I.: Angiology 10:311, 1959.	Postmastectomy thrombophlebitis of arm	10	3 asymptomatic; 5 improved; "offers promise...in this field"

***Reprints of these articles, as well as complete literature on intravenous fibrinolytic therapy with ACTASE, are available on request.**
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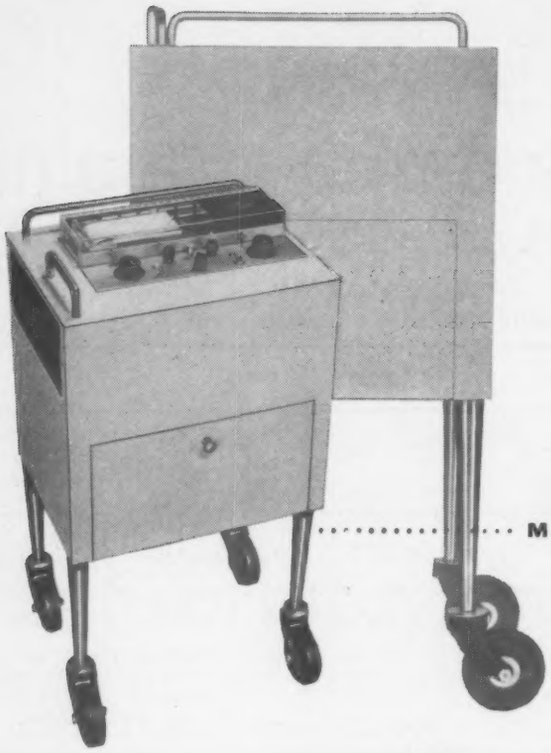

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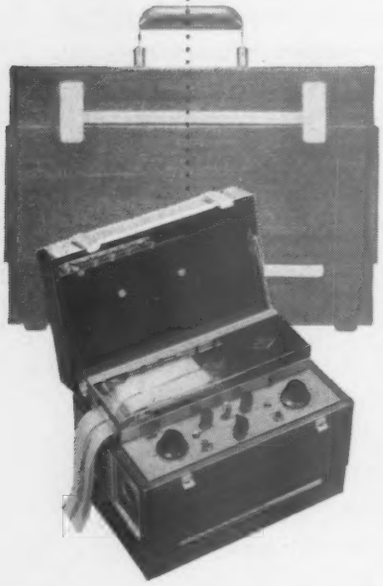

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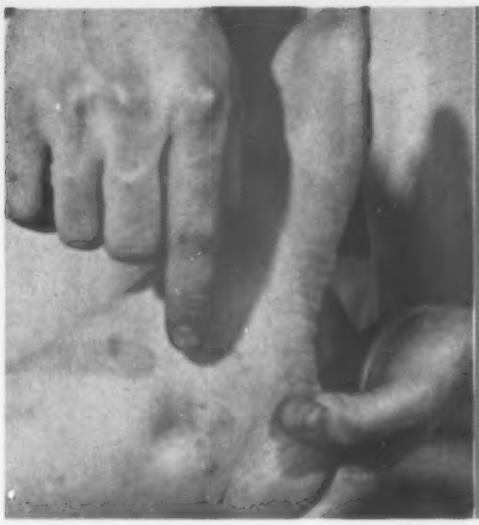
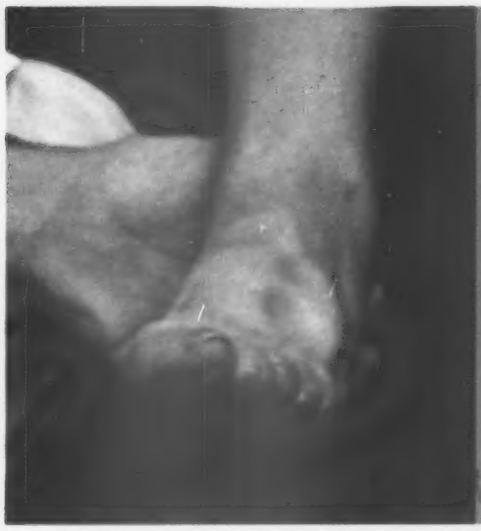
you get these results in case after case of edema and hypertension with **ESIDRIX®**

hospitalized patient with congestive heart failure



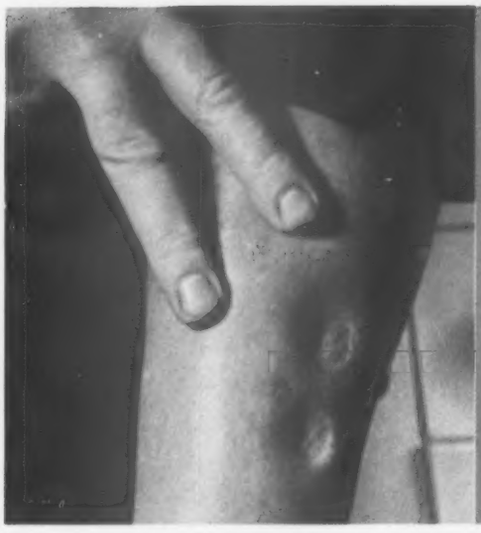
5 pounds lost in 4 days; 4+ pitting cleared; hepatic congestion and râles cleared; patient ambulatory

office patient treated for pedal edema and persistently high diastolic pressure

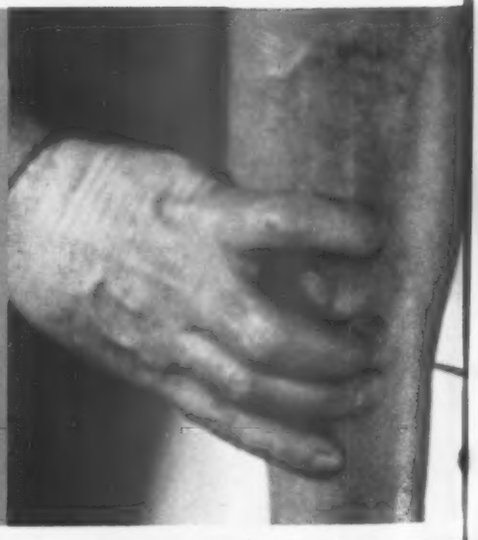


blood pressure reduced from 214/110 to 180/94 mm. Hg within 7 days with Esidrix (and Singoserp); pitting edema cleared

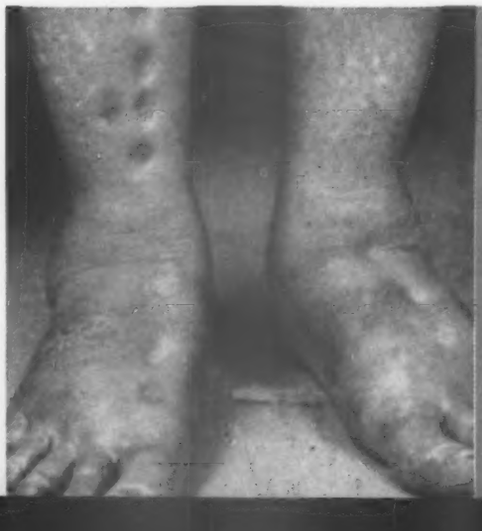
private patient with congestive heart failure; ascites and 4+ edema to the knee



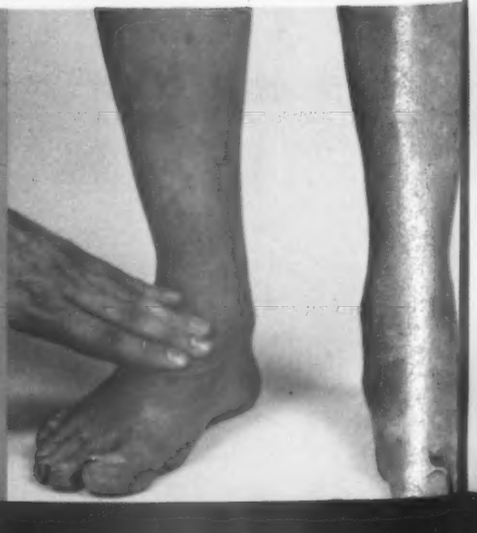
12½ pounds lost in 13 days; basilar râles and ascites no longer present; pitting edema of legs and feet cleared



hospitalized patient with Laennec's cirrhosis



27 pounds lost in 19 days; abdominal swelling and pedal edema cleared



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*Brest, A. N., and Likoff, W.: Am. J. Cardiol. *3*:144 (Feb.) 1959.

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hypertensive vascular disease
premenstrual edema
edema of pregnancy
steroid-induced edema
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SERPASIL® (reserpine CIBA)

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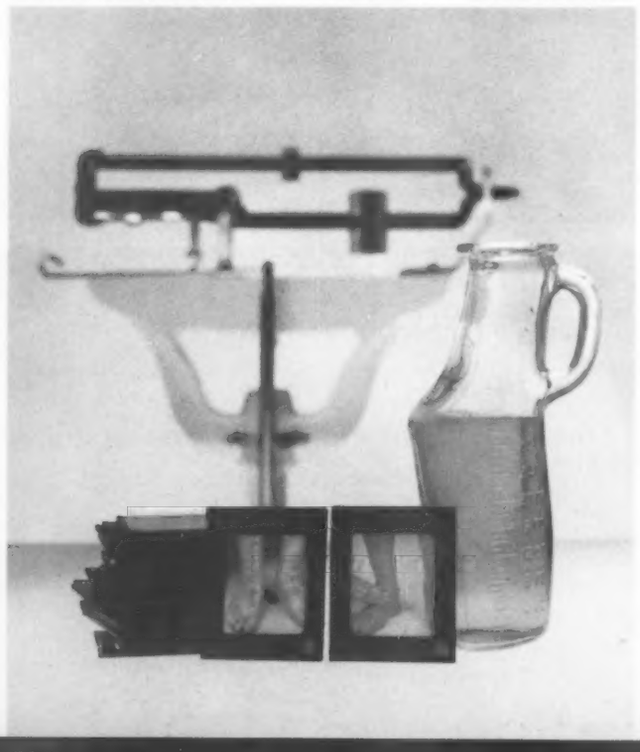

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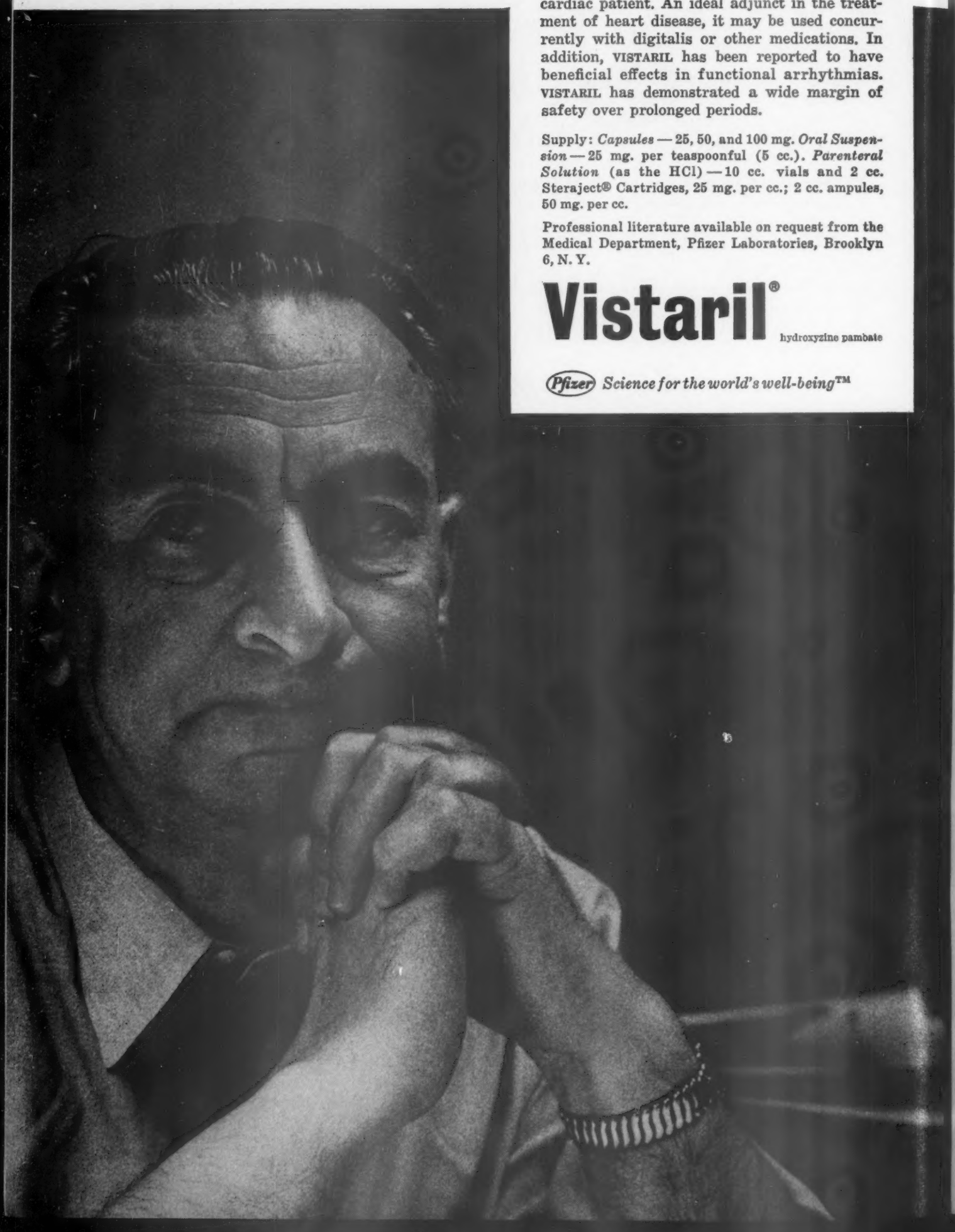

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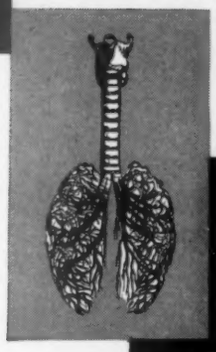

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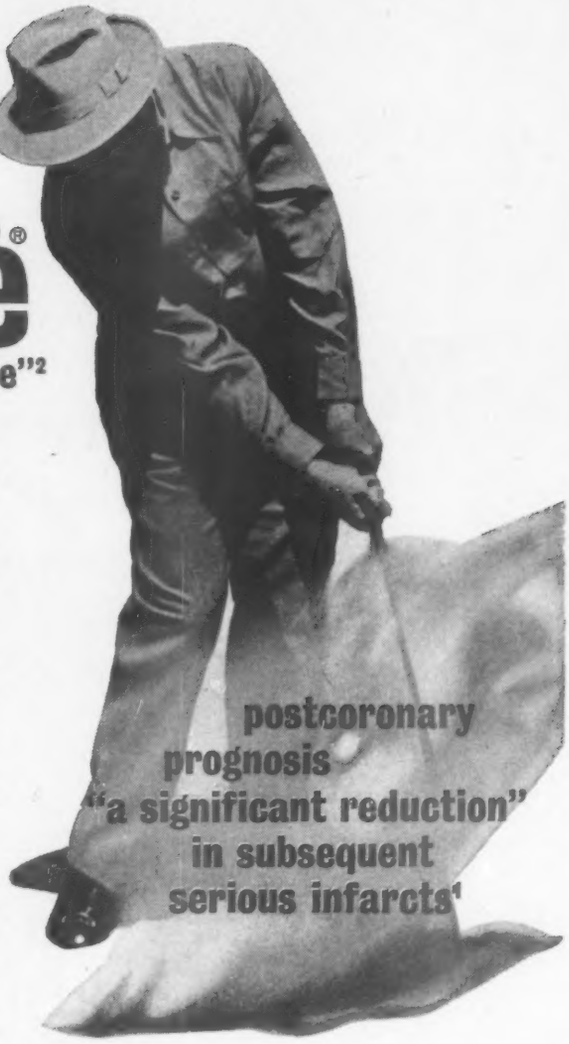

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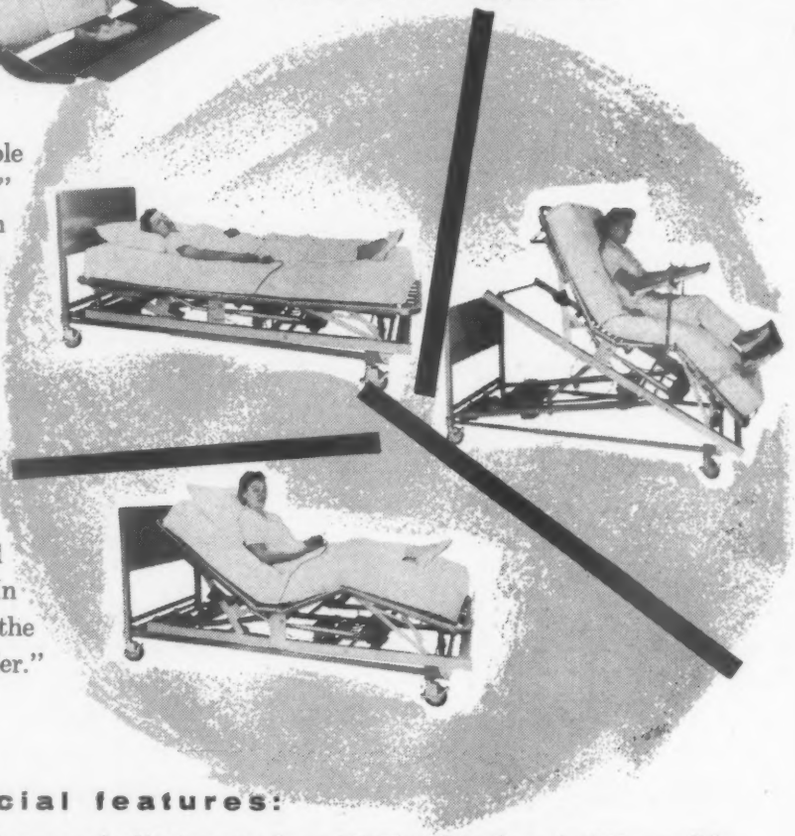

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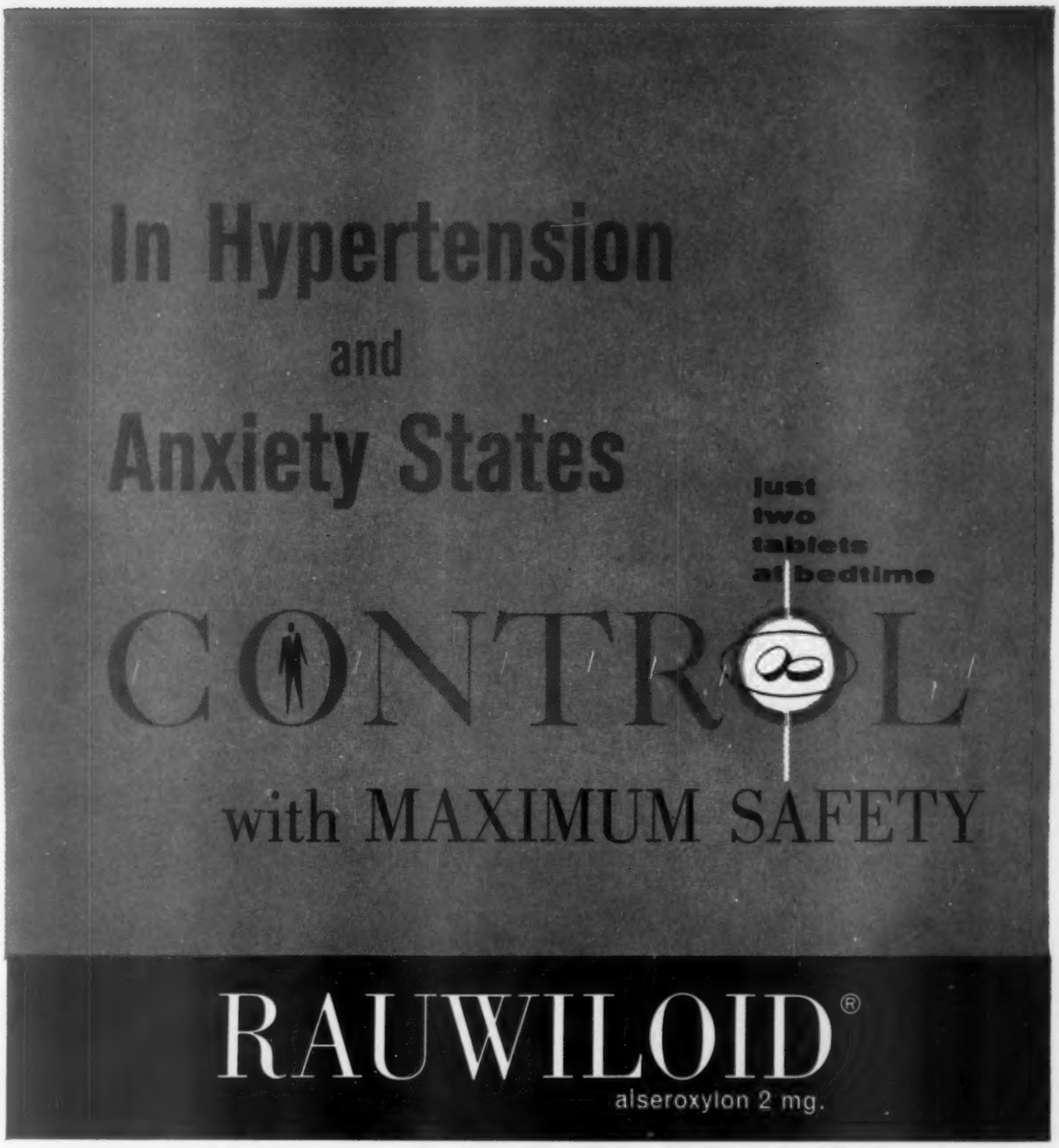

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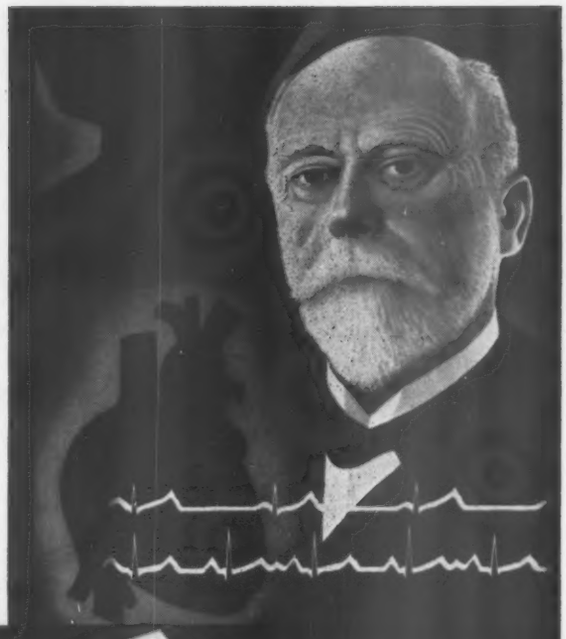

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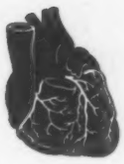

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1. Melville, K. I., and Lu, F.C.: Canadian M.A.J., *65*:11, 1951. 2. Bovet, D., and Nitti-Bovet, F.: Arch. Internat. de pharmacodyn. et therap., *83*:367, 1946. 3. Fuller, H. L., and Kassel, L.E.: Antibiotic Med. & Clin. Therapy, *3*:322, 1956.

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*Patent applied for

The American Journal of Cardiology

VOLUME V JUNE 1960 NUMBER 6

EDITORIAL

Treatment of Cardiovascular Emergencies

TREATMENT of cardiovascular and respiratory emergencies is of extreme importance. Adequate treatment can save the lives of many patients, who may gain useful years of fruitful activity if they survive an acute episode.

Treatment of this episode is an "emergency measure," which requires prompt decision, good judgment, adequate medical knowledge and often courage. Unfortunately, treatment of cardiovascular emergencies is often performed by the least experienced members of the medical profession (interns, medical clerks) or even by lay people (orderlies, nurses, policemen, firemen, relatives) who try to compensate for their lack of knowledge with good will and enthusiasm.

Sometimes the young physician has a few minutes or a few hours during which he may consult a handbook or manual. Even this interval is often deleterious because the syndrome may, in the meantime, progress to an irreversible stage. Moreover, information about emergencies is not easily available or requires skilled application to the individual case.

Another difficulty is represented by the fact that many physicians hesitate to treat a patient unless they have adequate information, have examined him and have formulated a diagnosis. Even though this orderly process is desirable, it is often too lengthy to be practical. Therefore, the physician should base his judgment on the necessity of treating the clinical syndrome or even the most dangerous or distressing symptoms at once, while basic treatment can be deferred until all necessary data have been gathered.

ETIOLOGY

The following basic syndromes belong to "cardiovascular emergencies."

(*1*) *Paroxysmal Systemic Hypotension:* This may be caused by various mechanisms and obviously presents various degrees of severity.

One possibility is that of *syncope*, which may be caused by emotion, a vasovagal attack, an episode of paroxysmal tachycardia or atrial flutter, sudden A-V block with ventricular arrest, total cardiac arrest, or may be an episode related to severe decrease of cardiac output in connection with aortic stenosis or ball-valve thrombus of the left atrium.

So-called *cardiogenic shock* may be related to many of the aforementioned conditions or may be due to myocardial infarction or massive pulmonary embolism.

Peripheral vascular collapse may be connected with reflex dilatation of the systemic vessels (emotion, vasovagal episode), depression of the vasomotor center (infections) or the complex mechanism of peripheral shock (allergic, traumatic, surgical, etc.).

Hemorrhagic shock may be the result of a stab or bullet wound severing an artery or penetrating the heart, or the rupture of esophageal (cirrhosis of the liver) or bronchial (mitral stenosis) varices. It also may be caused by gastrointestinal bleeding.

Finally, a *cerebrovascular attack* may be followed by a severe drop in blood pressure.

(*2*) *Paroxysmal Systemic Hypertension:* This may be an episode in the clinical course of pheochromocytoma. It may represent accentuation of a previously elevated blood pressure (essential or secondary hypertension, malignant hypertension). It often is the result of a cerebrovascular attack.

(3) *Paroxysmal Dyspnea with Hypoxia:* One common episode is *paroxysmal cardiac dyspnea.* Here the episode seems to be elicited by severe engorgement of the pulmonary vessels. Most forms occur in patients with previously elevated pulmonary arterial and venous pressures (mitral valve block). Others are caused

by left ventricular strain (severe systemic hypertension, aortic stenosis, coarctation) or left ventricular damage (myocardial infarction).

Another possibility is *paroxysmal pulmonary edema*, which has a more varied etiology and pathogenesis. In this syndrome, obstruction of the bronchiolar airways and of the alveolar cavities by foam aggravates the hypoxia.

A different mechanism is involved whenever there is *bronchial spasm* and *edema* of the bronchial mucosa (spastic bronchitis, bronchial asthma). Finally, a further possibility is represented by obstruction of a branch of the pulmonary artery (pulmonary embolism).

(4) *Sudden Episode of Precordial Pain:* Precordial pain of sudden onset and long duration may be connected with coronary occlusion or dissection of the aorta. Pulmonary embolism usually causes pain in the chest. Pericarditis, pleurisy and other conditions usually cause different and less excruciating pain.

(5) *Sudden Vascular Block:* The most typical, but less common, episode is represented by a saddle embolus of the aorta while peripheral embolism is less dramatic and more common.

Treatment

Several developments in the field of therapy give hope that many of these episodes can be successfully treated in an early stage.

(1) *Deep Central Sedation:* Sedation by administration of morphine, Demerol® or other drugs is indicated whenever pain, hypertension or dyspnea are present. An exception is represented by bronchial asthma (where depression of the respiratory center is detrimental). In patients in whom pain or dyspnea is associated with shock, or in whom there is cerebral edema, sedative agents should be administered more cautiously to avoid aggravation of shock through decrease of venous return and to avoid central depression and more severe cerebral edema. This applies particularly to morphine. Deep sedation should be considered not only an humanitarian procedure but also an essential part of treatment because relief of anxiety with its secondary vasoconstriction, blocking of autonomic reflexes and decrease of venous return obtained by administration of sedative agents contribute to relief of the attack.

(2) *Antifoaming Therapy (with Alcohol-Oxygen Vapor or Alcohol Aerosol):* This is indicated in all patients with pulmonary edema because it decreases the blocking of the airways by protein foam. Further treatment will be based on a complete evaluation of the mechanism of the attack and will often include the use of morphine, phenobarbital and Arfonad® (a sympatholytic drug). As previously stated, patients in shock or with progressive drop of blood pressure should be treated differently. When shock and pulmonary edema are both present, the basic drug and physical therapy is that of shock (see section on hypertensive therapy) while a propped-up position, administration of oxygen-alcohol vapors and intermittent inspiratory positive pressure respiration will decrease the dangers of pulmonary edema.

(3) *Hypertensive Therapy:* Intravenous infusion of physiologic glucose solution and administration of vasopressor drugs are currently used in cases of peripheral or cardiogenic shock without cardiac arrest. Restoration of blood volume can be obtained through administration of whole blood, plasma, plasma expanders or slow drip of physiologic salt or glucose solution. *Vasopressor drugs* include norepinephrine (Levophed®), mephentermine (Wyamine®) and metaraminal (Aramine®). In cases of vasomotor collapse, administration of Metrazol,® a respiratory and circulatory stimulant, seems preferable to administration of the sympathomimetic amines. If there is cardiac arrest, a different approach is indicated (see section on artificial electric pacemaker).

(4) *Hypotensive Therapy:* Intravenous infusion of drugs which depress the autonomic ganglia or dilate the peripheral vessels is frequently resorted to in cases of paroxysmal hypertension. In the dramatic crisis, slow intravenous drip of hexamethonium (Methium®) or pentolinium (Ansolysen®) is indicated (norepinephrine should be available in order to counteract a possible excessive drop in blood pressure). In the less severe crisis, reserpine and hydralazine (Apresoline®) usually are adequate and obtain the desired drop in blood pressure.

(5) *Anticoagulants:* Intravenous or intramuscular administration of *heparin* is used in the initial treatment of most patients with coronary, cerebral or peripheral thrombosis and seems to increase survival. *Fibrinolytic agents* are in the experimental stage and may offer further hope in the early treatment of these acute syndromes.

(6) *Artificial Electric Pacemaker:* This should be employed in cases of cardiac or ventricular arrest; *a defibrillator and a pacemaker* should be used in cases of ventricular fibrillation.

(7) *Antiarrhythmic Drugs:* In cases of *supraventricular* tachycardia, stimulation of the vagus nerve by either reflex maneuvers or by intravenous digitalization should be carried out. In cases of atrial flutter, digitalis may be administered even in toxic doses. In cases of atrial fibrillation, quinidine should be administered. This same drug should be administered in the other cases if previous therapy was ineffective. In cases of *ventricular* tachycardia or arrhythmia, procaine amide (Pronestyl®) should be given by slow intravenous drip. Neo-Synephrine® or other drugs which raise arterial blood pressure are sometimes administered and succeed in abolishing the tachycardia by improving coronary flow. Intravenous administration of potassium may be used as an extreme measure if the tachycardia was caused by digitalization.

In cases of A-V block, infusions of atropine and isoproterenol (Isuprel®) are often useful. The latter increases the excitability of the conducting tissues and of the ventricular pacemaker. An artificial electric pacemaker has been successfully employed in the dangerous transitional periods until an idioventricular pacemaker becomes effective.

(8) *Other Measures:* All the aforementioned drugs and procedures (some new, some known to cardiologists for a long time) give hope of saving a great number of lives if timely and correctly used.

The importance of *decubitus* should be emphasized in any emergency treatment. In cases of coma, syncope or shock from whatever cause (with a few exceptions), the patient should lie in a *supine position* in order to obtain an increase of blood flow to the brain.

In cases of *dyspnea*, regardless of cause, the patient should be placed in a *sitting position* to decrease venous return and diminish the load placed on the heart. (A theoretical exception is represented by cases of chronic cor pulmonale but, even in such cases, patients with dyspnea feel better in a sitting position.)

Hospital Program for Emergency Cases

Because emergency treatment should be given only by trained personnel, hospital and medical authorities should undertake the two following programs:

(1) Create an *emergency team* within the hospital. This should include medical and surgical personnel, nurses and non-professional skilled personnel. Members of the team and emergency apparatus should be available at all times.

(2) A special team composed of a doctor, a nurse and a technician should be placed in *each ambulance*, so that "emergency treatment" would start at the scene of the emergency and continue en route to the hospital. At present, hours of unnecessary delay elapse before the patient reaches the stage of actual and correct treatment.

We know of a small hospital, provided with several ambulances, created by a group of doctors in Brazil for the specific purpose of handling cardiovascular emergencies. The members of that team have probably saved more lives than the more numerous staffs of large hospitals of the same city.

Aldo A. Luisada, M.D., F.A.C.C.
Division of Cardiology
The Chicago Medical School
Chicago, Illinois

Clinical Studies

Ejection Time in Aortic Stenosis and Mitral Stenosis

Comparison Between the Direct and Indirect Arterial Tracings, with Special Reference to Pre- and Postoperative Findings*

ALBERTO BENCHIMOL, M.D., E. GREY DIMOND, M.D., F.A.C.C. *and* YEN SHEN, M.D.†

Kansas City, Kansas

CHANGES in arterial pulse contour accompanying heart disease have been recognized for some years,[1–13] particularly in relation to lesions of the aortic valve.[14–25] Despite this recognition, arterial tracings are employed by few investigators. Systematic consideration of changes in pulse contour have not been made in relation to mitral valve disease.

The purpose of this report is to investigate the abnormalities of the indirect carotid tracing in patients with aortic stenosis and mitral stenosis and to correlate these findings with the physiologic data obtained at cardiac catheterization and with pressures obtained at surgery. It is also our purpose to correlate the findings in the indirect carotid tracing with direct curves obtained during left heart catheterization or surgery.

MATERIAL AND METHODS

Technic: A cup applicator was applied over the carotid artery and connected by rubber tubing to a crystal pick-up microphone (Sanborn No. 374) which reproduces an electrical signal proportional to pressure change in the tubing. Frequency response of this crystal microphone is from 1 to 1,000 c.p.s. A descriptive detailed study of the electronic characteristics of this system has been presented by Miller and White.[26] To compare the fidelity of the system, our measurements in the indirect carotid tracing in patients with aortic stenosis were compared with the central aortic pressure curves obtained at left ventricular puncture or at surgery. In this particular group of patients the tracings were recorded with the PolyViso (Sanborn) with a Statham strain gauge No. T-23D. A phonocardiogram was recorded simultaneously, using a Sanborn microphone (62-1500-C-10). The tracings were recorded with the Twin Beam phonocardiograph at a paper speed of 75 mm. per second. The right carotid artery at the level of bifurcation was used in all cases. Recordings were made with the patient sitting with the head elevated approximately 45 degrees.

Case Material: The carotid tracing records of 486 patients with mitral valve disease and 239 patients with aortic stenosis were evaluated and screened. On the basis of diagnostic proof the following groups of patients were selected for further study. Only patients whose disease was confirmed by surgery or necropsy were included. Patients with questionable diagnosis or associated significant cardiac lesions were excluded from these studies.

Selection of patient material for this study was based entirely on the availability of documentation of the physiologic lesion. The thirty normal subjects were chosen on the basis of normal physical examination. In no case was the selection of the patient based on the adequacy of the carotid tracing. In addition the patient material represents consecutive patients subjected to cardiac surgery.

Group I was the control group and consisted of

* From the Cardiovascular Laboratory, Department of Medicine, University of Kansas Medical School, Kansas City, Kansas.

This study was supported in part by a Graduate Teaching Grant (HTS-5210 [C1]) in Cardiology from the National Heart Institute, and by funds from the Kansas Heart Association.

† Fellow in Cardiology, China Medical Board.

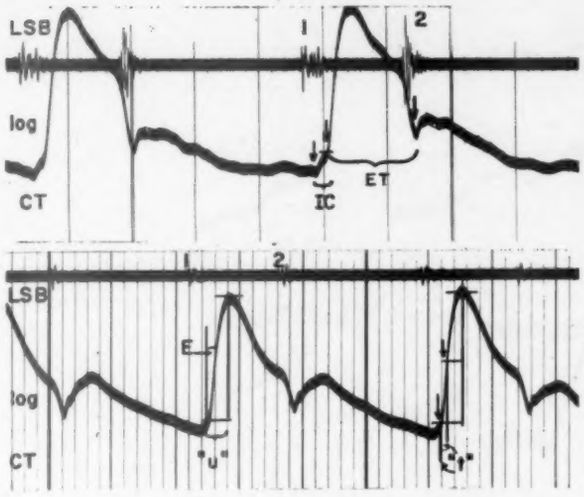

FIG. 1. Indirect carotid artery tracing showing how the total ejection time (ET), u time, t time and ejection angle (E) were measured. IC = isometric contraction.

thirty normal subjects; *Group II* consisted of forty patients with pure or dominant mitral stenosis; and *Group III* consisted of twenty-five patients with pure or dominant aortic stenosis.

All cases of mitral stenosis and sixteen cases of aortic stenosis were of rheumatic origin. The remaining cases of aortic stenosis were congenital, seven valvular and two infundibular, the latter confirmed by surgery and necropsy.

All twenty-five cases of aortic stenosis were confirmed at surgery and further by postmortem examination in eight. In twenty-two patients a significant pressure gradient across the aortic valve was present. In three patients pressures were not recorded, but significant stenosis was demonstrated at surgery.

The analysis of the carotid tracing was made in each case with special attention to the duration of the total ejection time and the upstroke time. The former is measured from the initial rise of the upstroke to the dicrotic notch and does not include isometric contraction; the latter ("u" time*) from the beginning of the ascending limb to the peak of the pulse wave (Fig. 1). As described by Duchosal,[19] "t" time† was calculated by drawing a line from onset of ejection (excluding the isometric contraction) to the top of the ascending limb and measuring half of the vertical line (Fig. 1). The ejection angle was calculated according to the criteria of Daoud et al.,[20]

* Upstroke time.

† Half of the ascending limb of the carotid tracing.

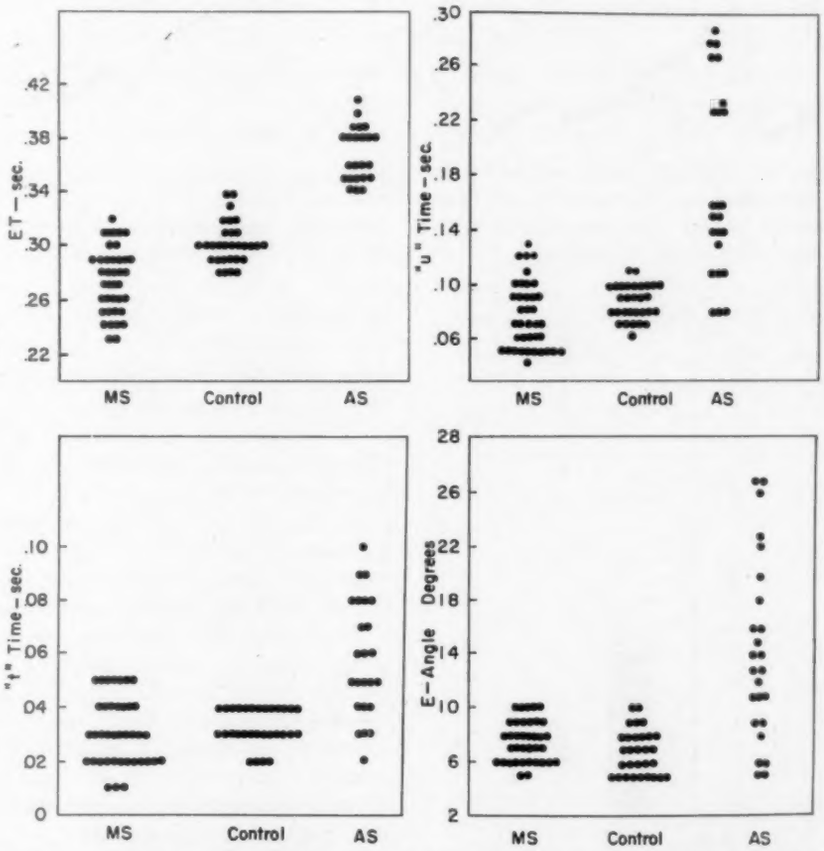

FIG. 2. Frequency distribution of total ejection time, u time, t time and ejection angle (E) in normal subjects, and in patients with mitral stenosis and aortic stenosis. See text.

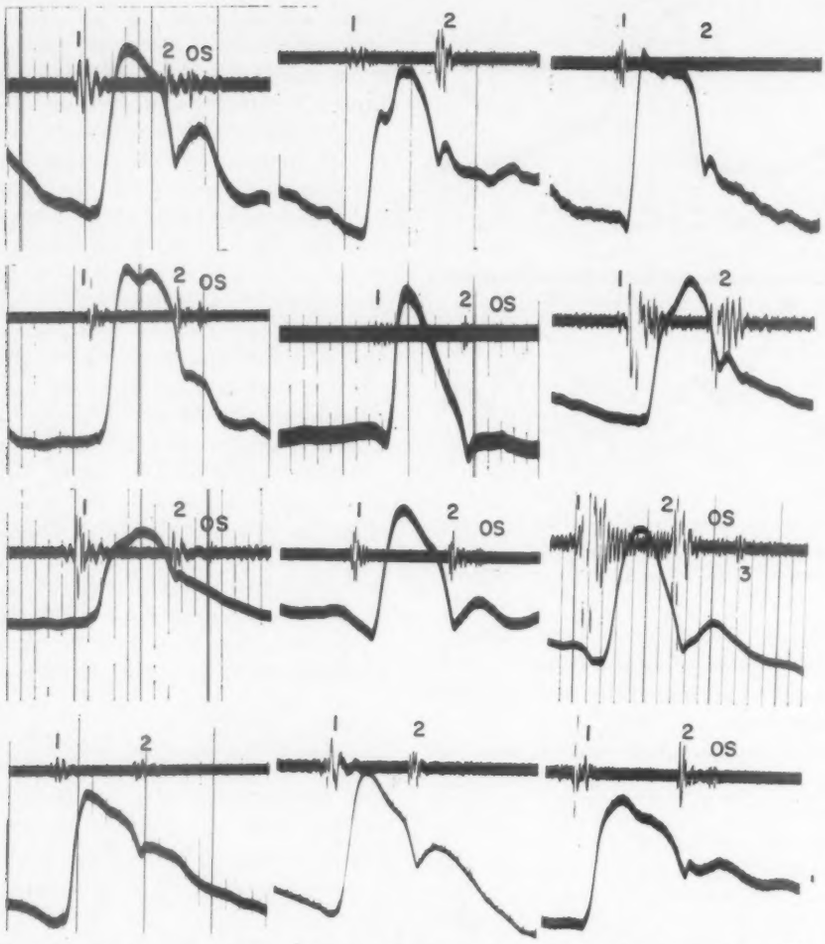

FIG. 3. Indirect carotid tracing in twelve patients with mitral stenosis. Abnormalities are discussed in the text. Phonocardiograms were taken at left sternal border with logarithmic technic. Note the rapid ascending limb and shortening of the total ejection time (ET). OS = opening snap.

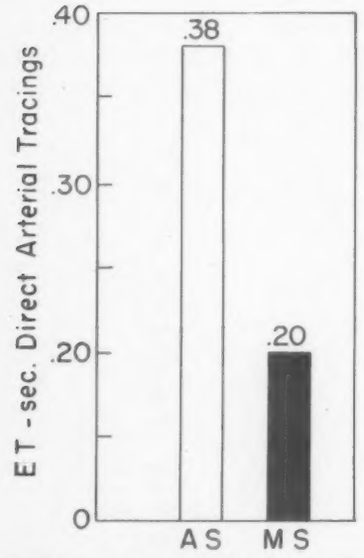

FIG. 4. Total ejection time (ET) in direct arterial tracings in patients with aortic stenosis and mitral stenosis. See text.

measuring the angle that the ascending limb makes with the vertical line. A previous report[27] detailed a complete phonocardiographic study of this group of patients with mitral stenosis.

Mitral and aortic valve size were estimated at the time of surgery, and in some cases calculated using Gorlin's formula[28,29] with data from right heart catheterization. Right ventricular, pulmonary artery and pulmonary "wedge" pressures and physiologic data were determined during routine right heart catheterization with the technics previously described.[30]

Percutaneous left ventricular puncture was performed prior to surgery in seven patients with aortic stenosis by the technic described by Brock.[31] Pre- and postoperative pressures were obtained at surgery in seventeen patients. A complete study of the carotid tracing was performed pre- and postoperatively in seventeen patients with aortic stenosis and in eighteen patients with mitral stenosis.

All reported intervals and angles represent the mean values of measurements made in five cardiac cycles. All measurements were corrected for the

TABLE I
Analysis of Measurements of the Carotid Tracings*

Group and No.	Total Ejection Time (sec.)		u Time (sec.)		t Time (sec.)		Ejection Angle (degrees)	
	Range	Average	Range	Average	Range	Average	Range	Average
Control, 30	0.28–0.34	0.302 ± 0.017	0.06–0.11	0.008 ± 0.013	0.02–0.04	0.033 ± 0.007	4.6–10.3	6.86 ± 1.51
Mitral stenosis, 40	0.23–0.32	0.274 ± 0.024	0.04–0.13	0.075 ± 0.057	0.01–0.04	0.031 ± 0.013	4.9–11.9	7.91 ± 1.92
Aortic stenosis, 25	0.31–0.41	0.364 ± 0.031	0.08–0.29	0.179 ± 0.071	0.02–0.10	0.059 ± 0.021	4.8–2.73	14.29 ± 5.75

NOTE: In the "average" columns, the figure under the ± sign is the standard deviation.
* The values were corrected for the heart rate.

heart rate, dividing the value obtained in the tracings by the square root of the cycle length. Vertical lines in the tracings are 0.04 second apart.

RESULTS

GROUP I: CONTROL GROUP (THIRTY CASES)

The total ejection time ranged from 0.28 to 0.34 second (0.302 ± 0.017 second); the t time ranged from 0.02 to 0.04 second (0.033 ± 0.007 second); the u time ranged from 0.06 to 0.11 second (0.088 ± 0.013 second). The ejection angle ranged from 4.6 to 10.3 degrees (6.86 ± 1.51 degrees) (Table I, Fig. 2).

GROUP II: MITRAL STENOSIS (FORTY CASES)

The carotid tracing in this group revealed a total ejection time ranging from 0.23 to 0.32 second (0.274 ± 0.024), significantly below the limits of the control group (level of significance of $p < 0.001$)[32] (Table I, Fig. 2). The t time in the whole series averaged slightly below the normal values (0.031 ± 0.013 second), and the ejection angle (4.9 ± 1.19 degrees) as well as the u time and t time were statistically not significantly different ($p = 0.90$ and 0.50, respectively) when compared with the control group.

There were eighteen patients with a normal sinus rhythm and twenty-two with auricular fibrillation. Auricular fibrillation was associated with a somewhat shorter ejection time in comparison with the group with normal sinus rhythm.

The carotid tracing showed a rapid ascending limb, without a significant plateau, with a distinct dicrotic notch (Fig. 3). Ejection time measured in the direct arterial tracings averaged a similar value to that recorded by the indirect method (Fig. 4).

A reasonably good correlation could be established between the total ejection time and the left ventricular stroke volume and cardiac output. With decrease in the cardiac output and stroke volume there was a reduction in the total ejection time (Fig. 5).

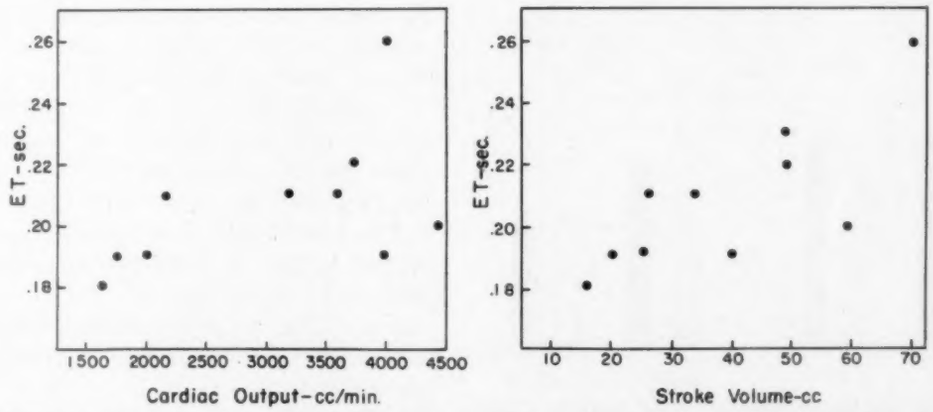

FIG. 5. Mitral stenosis. Total ejection time (ET)-cardiac output correlation, and total ejection time (ET)-stroke volume correlation.

TABLE II
Mean Value of Measurements of the Indirect Carotid Artery Tracings Pre- and Postoperatively*

	Total Ejection Time (sec.)	u Time (sec.)	t Time (sec.)	Ejection Angle (degrees)
		Mitral Stenosis (18 cases)		
Preoperative	0.277 ± 0.024	0.076 ± 0.02	0.033 ± 0.017	7.0 ± 1.90
Postoperative	0.304 ± 0.023	0.078 ± 0.023	0.030 ± 0.009	8.3 ± 2.28
		Aortic Stenosis (17 cases)		
Preoperative	0.360 ± 0.024	0.187 ± 0.064	0.059 ± 0.022	14.66 ± 6.91
Postoperative	0.316 ± 0.039	0.116 ± 0.033	0.046 ± 0.011	10.15 ± 2.92

NOTE: In this table, the figure to the right of the ± sign is the standard deviation.
* The values were corrected for the heart rate.

MITRAL STENOSIS: PRE- AND POSTOPERATIVE FINDINGS

Eighteen patients were studied. The total ejection time ranged from 0.23 to 0.31 second (0.277 ± 0.024 second) preoperatively and from 0.26 to 0.36 second (0.304 ± 0.023 second) postoperatively (Fig. 6).

A correlation was made between the total ejection time and the size of the mitral valve before and after valvulotomy as reported by the surgeon. In seventeen patients (94 per cent) the increase in the size of the mitral orifice after surgery was accompanied by an increase in duration of the total ejection time (Fig. 7). No significant changes occured in the postoperative t time, u time and ejection angle (Table II). The study of the apex cardiogram in this group of patients, as reported previously,[27] revealed a significant increase in early left ventricular filling as reflected by the appearance of a rapid filling wave in the postoperative apex cardiogram. In this same group of patients a determination of the rapid descent of the V wave in the left atrial curves revealed a more rapid left atrial emptying with a high Ry/V ratio, according to the criteria of Owen and Wood.[33]

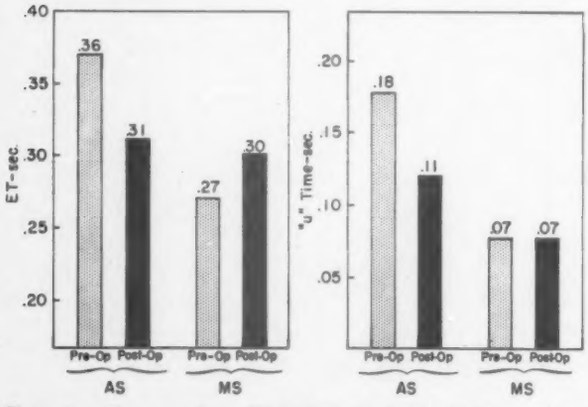

FIG. 6. Pre- and postoperative total ejection time (ET) and u time in patients with aortic stenosis and mitral stenosis.

Special attention was given to the presence of heart failure in this group, since heart failure can decrease the duration of left ventricular ejection by decreasing the cardiac output. None of these patients had clinical evidence of heart failure, although they were maintained on digitalis.

GROUP III: AORTIC STENOSIS (TWENTY-FIVE CASES)

The carotid tracing was abnormal in all patients, revealing, in general, a slow ascending limb, prominent anacrotic notch, carotid shudder, systolic plateau with and without a distinct dicrotic notch (Fig. 8).

Total Ejection Time: In all patients the total ejection time was greater than 0.30 second being consequently above the average of the total ejection time in all patients (Table I, Fig. 2). In the whole series it ranged from 0.31 to 0.41 second (0.364 ± 0.031 second) which was significantly greater than the values in the control group (0.302 ± 0.017 second) (Fig. 9). This difference was statistically significant with p less than 0.001.

t Time: The t time ranged from 0.02 to 0.10 second (0.06 ± 0.021 second) (Table I). This

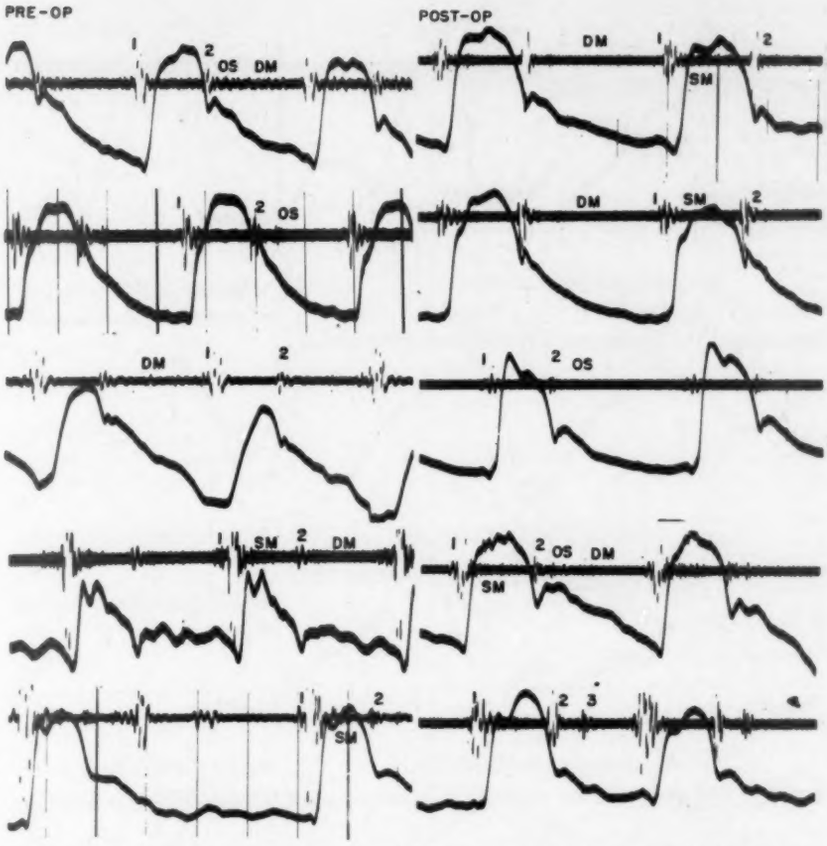

FIG. 7. Pre- and postoperative tracings in five patients with mitral stenosis. Note decrease in the total ejection time in the preoperative tracings. After mitral valvulotomy there is an increase in the total ejection time. Sound tracings were taken at the left sternal border (fourth intercostal space) with logarithmic technic.

value was above the average of the control group (0.033 ± 0.007 second) (Fig. 2). Considering 0.04 second as the upper limit of normal for the t time, it is concluded that seven patients of twenty-five presented t times from 0.02 to 0.04 second (28 per cent) and the remaining eighteen patients (72 per cent) presented abnormally prolonged t times (0.05 to 0.10 second).

Ejection Angle: The ejection angle in this series ranged from 4.8 to 27.3 degrees (14.29 ± 5.75 degrees) (Table I). This was considerably higher than the average of the control group (6.86 ± 1.51 degrees). In our control series the upper limit of normal is 10 degrees. Thus, seven patients of twenty-five presented an ejection angle below 10 degrees (28 per cent) and the remaining eighteen (72 per cent) presented an ejection angle above the normal limits.

Upstroke Time: The u time varied in this group from 0.08 to 0.29 second (0.179 ± 0.071 second), although only two patients presented u times below 0.11 second (Table I). The range of normal as determined in the control group was 0.06 to 0.11 second with an average of 0.088 second. This difference when compared with the control group was statistically significant, with the level of significance of p being less than 0.001.

From these observations it was noted that the duration of the total ejection time was abnormal in all patients, the u time in 92 per cent, and the t time and the ejection angle in 72 per cent of patients, respectively.

Direct Aortic Pressure Curves: In twenty patients the central aortic pressure curves obtained at surgery could be analyzed. In the remaining five patients the presence of artefacts made the analysis impossible. The ejection angle was not determined in this group of patients because of different speeds used to record the tracings.

The total ejection time could be measured in only thirteen patients; it ranged from 0.28 to 0.52 second (0.38 ± 0.06) (Fig. 10). The

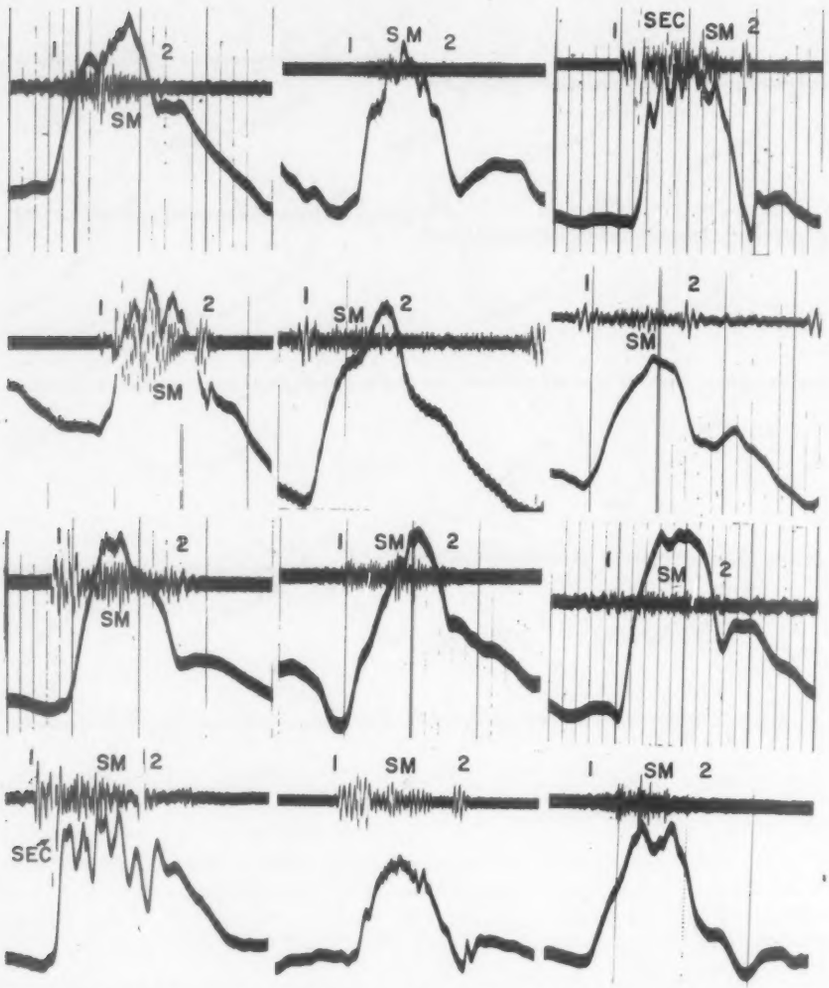

FIG. 8. Indirect carotid tracing on twelve patients with aortic stenosis. Abnormalities are discussed in the text. All phonocardiograms were taken at the aortic area with logarithmic technic. SM = systolic murmur. SEC = systolic ejection click.

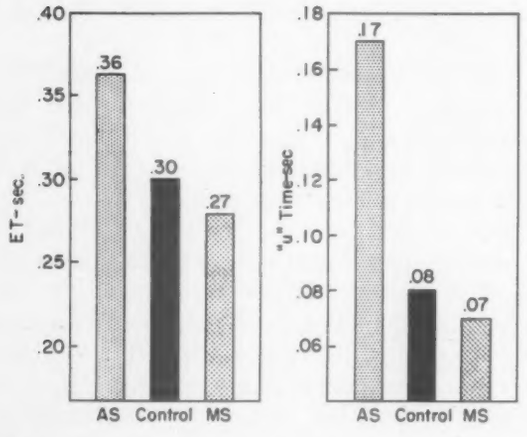

FIG. 9. Total ejection time (ET) and u time in normal subjects, and in patients with aortic stenosis and mitral stenosis. See text.

average in the direct aortic tracings was quite similar to that in the indirect carotid tracings (0.364 ± 0.031) and the difference was not statistically significant (Fig. 4). The u time ranged from 0.10 to 0.36 second (0.24 ± 0.06 second). This value was significantly higher than the u time measured in the indirect carotid tracing (0.179 ± 0.071 second). The t time ranged from 0.04 to 0.19 second (0.11 ± 0.04 second), which was also higher than the measurements in the indirect carotid tracing.

Estimation of Degree of Severity: In estimating the degree of severity of the aortic stenosis, using the left ventricular-aortic pressure gradient and the surgeon's estimate of the size of the aortic valve as criteria, it was noted that the determination of the u time and total ejection time gave the most reliable correlation in our series (Fig. 11).

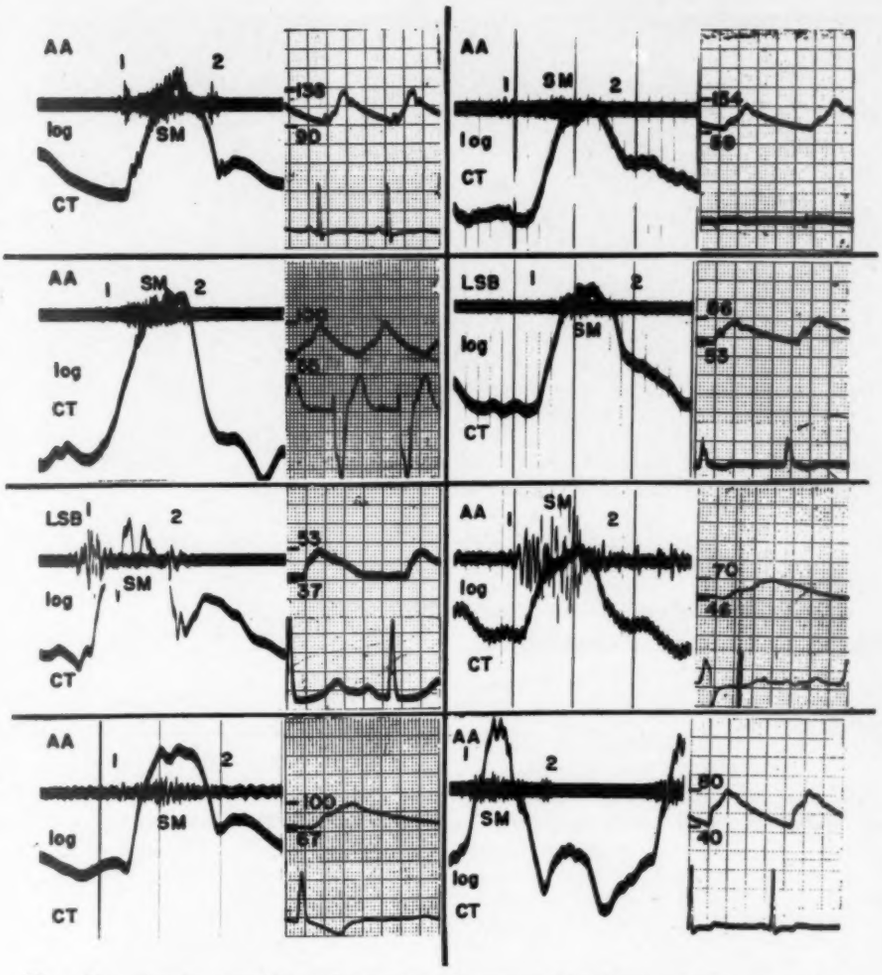

FIG. 10. Aortic stenosis. Comparison between the direct aortic curves and indirect carotid tracings in eight patients. AA = aortic area. LSB = left sternal border.

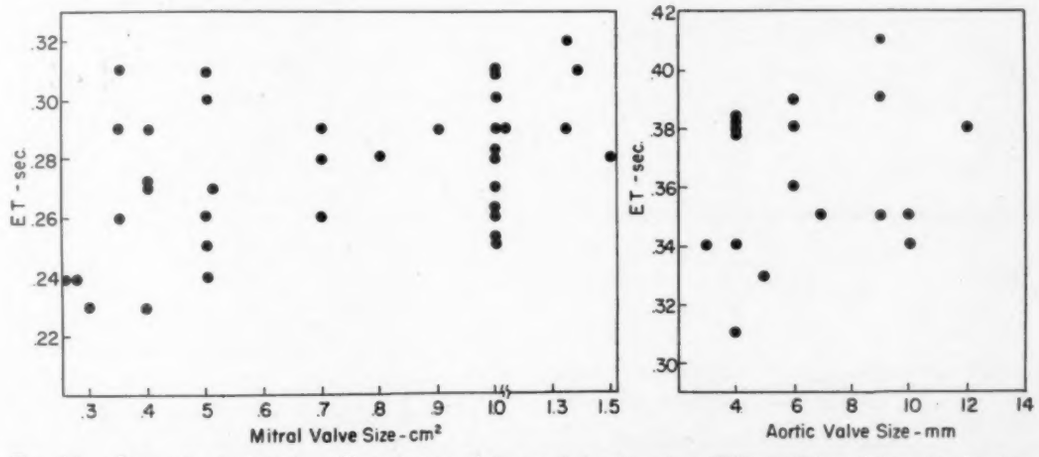

FIG. 11. *Left*, mitral stenosis. Correlation of the total ejection time (ET) and size of the mitral valve. *Right*, aortic stenosis. Correlation of the total ejection time (ET) and size of the aortic valve. See text.

From this observation it is suggested that the determination of severity may be made with some degree of accuracy using the total ejection time and u time as criteria.

AORTIC STENOSIS: PRE- AND POSTOPERATIVE FINDINGS

The carotid tracing was available for this study in seventeen patients in whom aortic

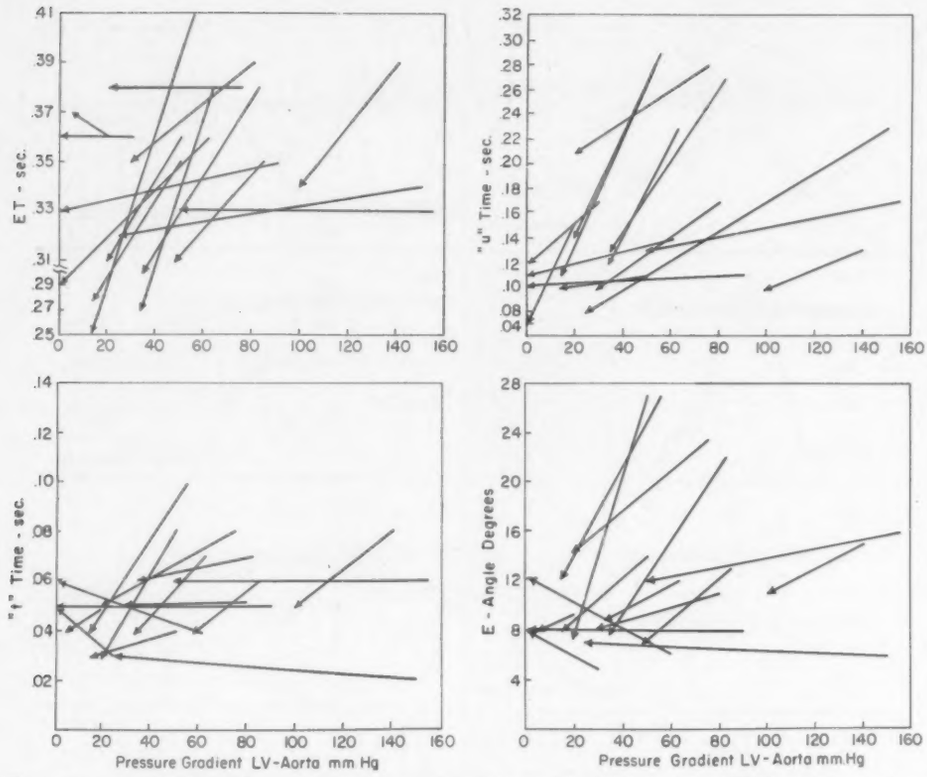

FIG. 12. Aortic stenosis. Pre- and postoperative total ejection time (ET), u time, t time and ejection angle in seventeen patients, correlated with left ventricular-aortic pressure gradient.

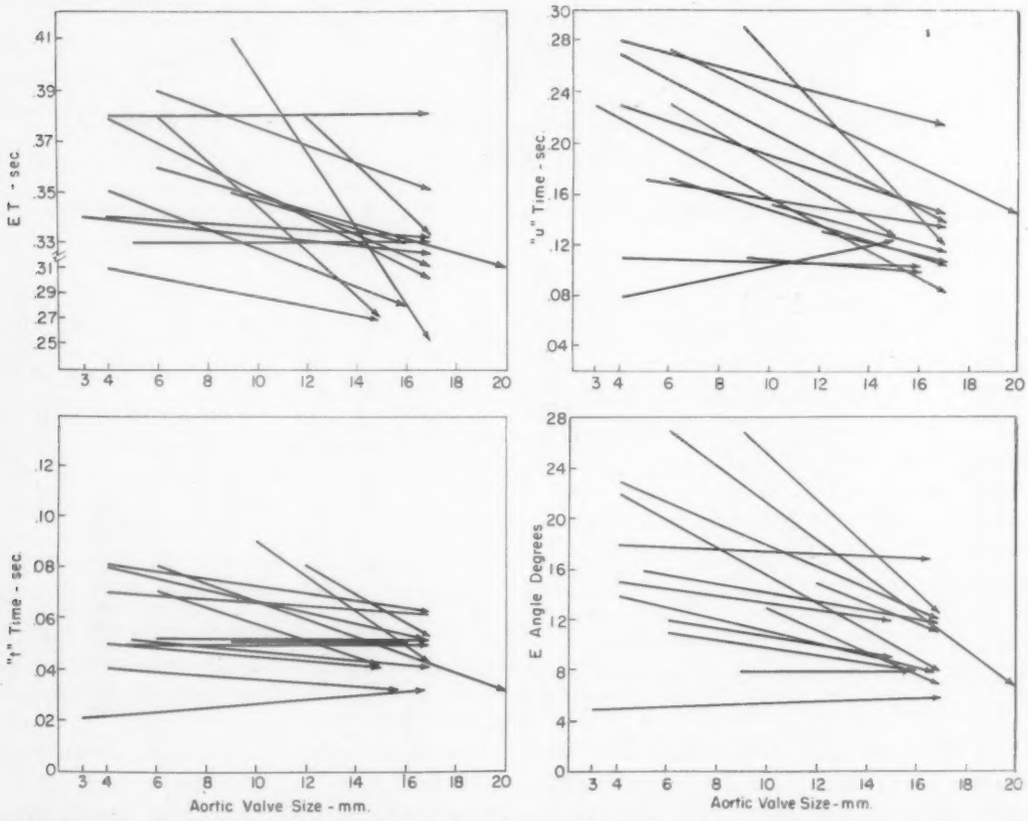

FIG. 13. Aortic stenosis. Pre- and postoperative total ejection time (ET), u time, t time and ejection angle in seventeen patients, correlated with the size of the aortic valve.

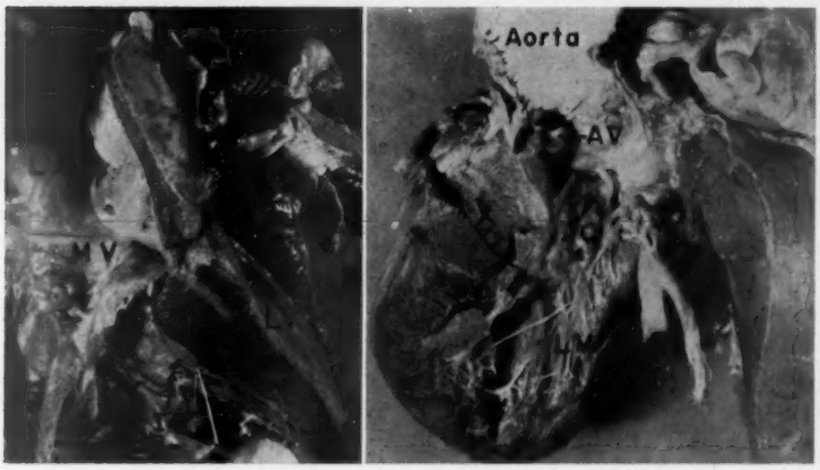

FIG. 14A. Congenital subaortic stenosis with normal aortic valve cusps. LA = left atrium. MV = mitral valve. IC = infundibular chamber. LV = left ventricle. AV = aortic valve.

valvulotomy resulted in significant reduction in pressure gradient and an increased size of the aortic orifice.

In this group the preoperative total ejection time varied from 0.31 to 0.41 second (0.360 ± 0.024 second) (Table II). Significant decrease in the total ejection time occurred in thirteen patients, was unchanged in three and increased in one (Figs. 12 and 13). The average postoperative total ejection time was 0.316 second (0.316 ± 0.039 second), ranging from 0.27 to 0.41 second (Fig. 6). Comparison between the pre- and postoperative sample revealed that the difference in the mean values was significant to a level of p = 0.005. The total ejection time at intervals to one year after surgery remained constant.

Postoperatively, the u time decreased significantly in all but one patient, as demonstrated in Figure 12. The average preoperative u time was 0.187 second (0.187 ± 0.064 second) and the postoperative average was 0.116 second (0.116 ± 0.033 second). This difference was statistically significant with a level of significance of p of less than 0.001. The t time decreased in twelve cases (80 per cent), remained unchanged in two and increased in three. The average preoperative t time was 0.059 second (0.059 ± 0.022 second) and the postoperative, 0.046 second (0.046 ± 0.011 second) (Fig. 12). The ejection angle decreased in eleven patients, remained unchanged in one and increased in three.

SUBAORTIC STENOSIS

Two cases of subaortic stenosis with a distinct infundibular chamber were identified at surgery and necropsy (Figs. 14A and 15). The type of stenosis was not diagnosed clinically. Both patients presented peculiar carotid tracings. They revealed a sharp and rapid ascend-

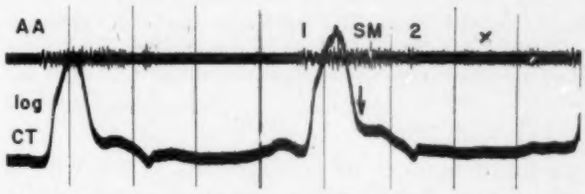

FIG. 14B. Subaortic stenosis (infundibular type). The indirect carotid tracing showed a peculiar contour as seen in Figure 15. Note the rapid ascending limb, normal t time, u time and ejection angle, and a late systolic wave (arrow) with marked prolongation of the total ejection time. X = artefacts.

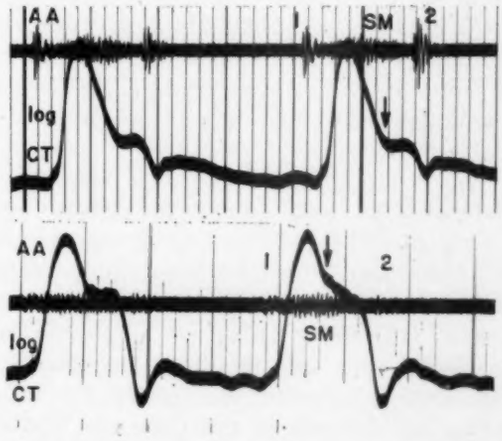

FIG. 15. Indirect carotid tracing in two patients with subaortic stenosis (infundibular type). Note normal t time, ejection angle and u time, and late systolic wave (arrow). The total ejection time in both tracings is markedly prolonged.

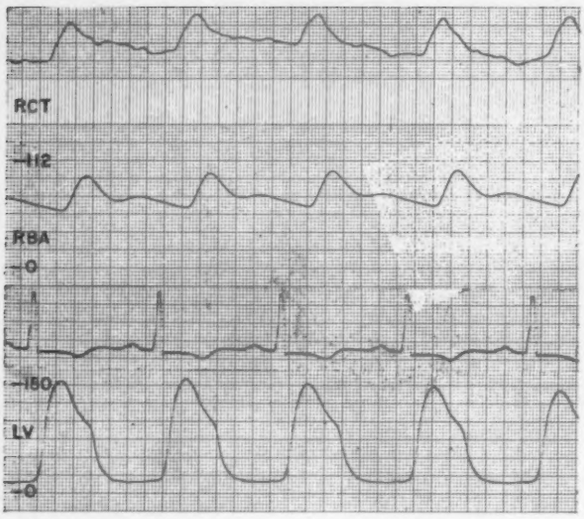

FIG. 16. Aortic stenosis. Indirect right carotid artery tracing (RCT) recorded simultaneously with the direct right brachial (RBA) and left ventricular (LV) pressure curves. Note the similarities in the indirect RCT with RBA tracing except for delay in the transmission of pulse wave.

ing limb, absence of an anacrotic notch with a subsequent late systolic wave and a distinct dicrotic notch. This pattern gave an appearance of a double systolic wave and marked prolongation of the total ejection time. A third patient (Fig. 15), (not included because of the lack of definite proof) also revealed the same contour seen in Figure 14B. This patient had clinical evidence of aortic stenosis. The ejection angle, t time and u time were within normal limits and the only abnormal finding was the prolongation of the total ejection time.

COMMENTS

Extensive clinical and experimental study has been directed toward arterial pulse recordings in the past.[34–42] Characteristic abnormalities of contour in the direct and indirect arterial tracings, although subject to some controversy,[24,25] are of generally accepted importance in the diagnosis of aortic lesions. Reports encountered in the literature correlating the duration of total ejection time with pressure gradient across the aortic valve are not common. The recent development of aortic valve surgery and the technic of left ventricular puncture has made this correlation possible.

The main criticism directed to the method of recording the indirect carotid tracing is the recording technic, which varies according to the frequency response of the system.[24] This frequency response in some recording instruments is non-linear below 30 c.p.s. This variation makes the comparison of the data of different investigators difficult. We believe the electronic characteristics of the crystal microphone, as demonstrated by Miller and White,[21] are satisfactory, and are convinced from the analysis of our data that a careful analysis of the indirect carotid tracing is of good practical value. Our belief is based on the significant percentage of abnormal tracings in aortic and mitral stenosis and also on the changes which occur after valvulotomy (Figs. 12 and 13).

As demonstrated in Figures 10 and 16, no appreciable difference could be demonstrated in curves recorded directly in the ascending aorta as compared with the curves recorded in the indirect carotid tracing, except for a somewhat greater u time in the former.

Aortic Stenosis: It has been well documented that significant reduction in the aortic valve orifice results in an increase in left ventricular pressure and a consequent increase in left ventricular work.[42] This results in prolongation of left ventricular systole and a delay in total ejection time. The characteristic features of pulse contour in aortic stenosis are: carotid shudder, prominent anacrotic notch, slow upstroke time, prolongation of the initial upstroke phase and prolongation of left ventricular systole.

In our series, additional information regarding the dynamics of the left ventricle was obtained by measuring the total ejection time, u time and t time in the aortic pressure tracings obtained during left ventricular puncture and at surgery. With t time and ejection angle as the only criteria, the diagnosis of aortic stenosis could have been made in only 72 per cent of patients. By determination of the total ejection time and the u time it was possible to make a presumptive diagnosis in 100 per cent and 82 per cent of patients, respectively.

The determinations of t time and ejection angle[19,20] are based on the fact that the greatest part of left ventricular output is discharged in the first half of ventricular systole. This statement, while grounded on a physiologic mechanism, excludes the fact that obstruction may continue to play an important part in late systole and gives rise to a late powerful contraction. This fact holds true in pulmonary stenosis,[43] for example, in which there is a powerful late right ventricular contraction as revealed by a late accentuation of the systolic

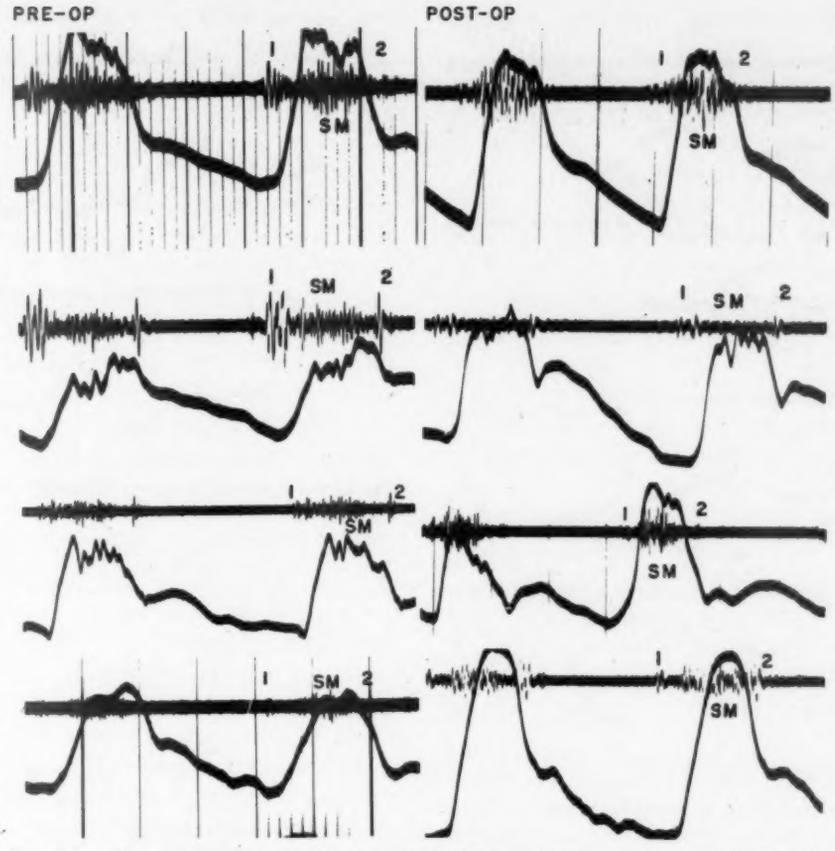

FIG. 17. Pre- and postoperative carotid tracings in four patients with aortic stenosis. Note remarkable change in the postoperative tracings. Phonocardiograms were recorded at the aortic area with logarithmic technic.

murmur and marked prolongation of right ventricular systole. It also should be mentioned that if the peculiar contour of the carotid tracing in subaortic stenosis (Figs. 14B and 15) proves to be a constant phenomenon, the t time and the ejection angle would be of no value in the diagnosis of this condition. The initial quick rising of the systolic upstroke in subaortic stenosis may be due to early emptying of the infundibular chamber.[46] It has been suggested, however, that in pulmonary infundibular stenosis,[44] an analogous situation, infundibular chamber contraction is late in systole and the initial quick rise may be due to high flow velocity. This is also supported by electrocardiographic studies with direct epicardial recordings. As demonstrated by Barbato et al.[45] in patients with infundibular stenosis, the infundibular chamber is the last part of the right ventricle to be activated. Thus, the delayed portion of the pulse wave in aortic infundibular stenosis probably represents flow during the late contraction of the infundibular chamber. This pulse wave pattern seems to be present only in cases of subaortic stenosis with an infundibular type of obstruction, since in one case of membranous type this pattern was not recorded in the carotid tracing. In this particular case the pulse wave contour was identical to that in acquired aortic valvular stenosis.

Although the central aortic pressure and peripheral arterial pressure are functions not only of the rate and pattern of ventricular ejection and stroke volume but also of the distensibility of the aorta, peripheral vascular resistance and viscosity of the blood, the statistically significant incidence of prolongation of the total ejection time as an isolated observation indicates that the method is of clinical value. Our data are in agreement with the measurements of Wood[17] recorded in direct arterial tracings and with those by Donoso et al.[47] obtained in indirect carotid tracings.

The pulse wave contour and duration of the total ejection time may be normal in some patients with mild or moderate aortic stenosis. Our patients represent examples of severe stenosis with clinical symptoms requiring aortic

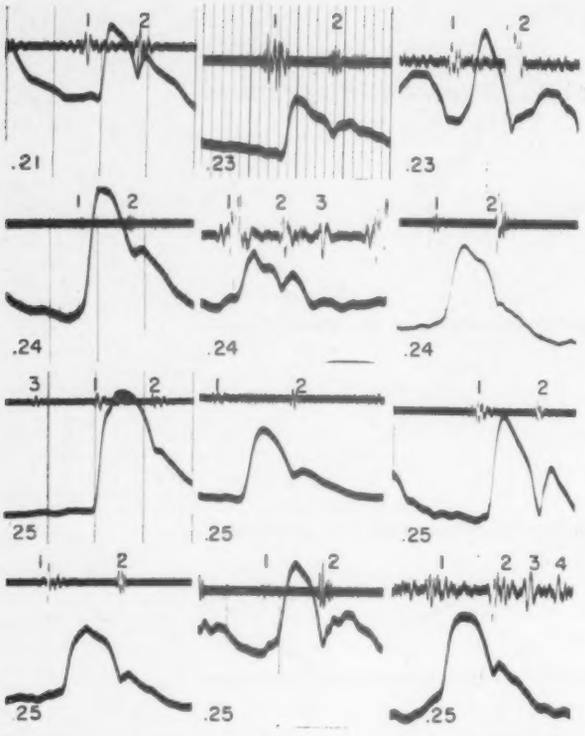

FIG. 18. Indirect carotid artery tracings in twelve patients with heart failure due to ischemic heart disease. Corrected total ejection time appears in lower left hand corner. Phonocardiograms were taken at the apex (stethoscopic technic). Note decrease in the total ejection time in all patients.

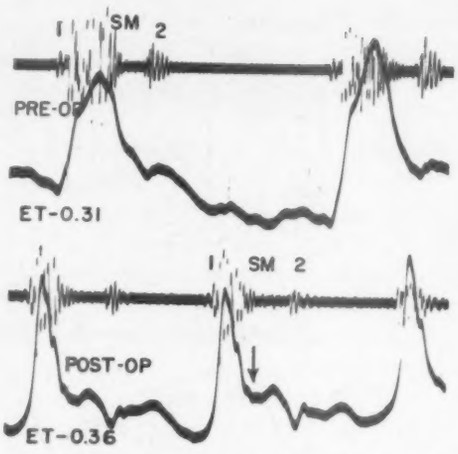

FIG. 19. Aortic stenosis (valvular type). *Top*, preoperative carotid tracing showing prolongation of the total ejection time (ET) and a high anacrotic notch. *Bottom*, postoperative carotid tracing showing early systolic peak, double systolic wave and marked prolongation of the total ejection time (ET). The tracing is similar to that seen in subaortic stenosis. Compare with Figures 8 and 15.

valvulotomy and thus represent a selected population of moderate or severe aortic stenosis. This fact does not invalidate the method, since it is in this group that a careful evaluation with clinical and laboratory methods is needed.

Smith et al.[24,25] suggested that the measurements made in the indirect carotid tracing will be of no value in assaying aortic stenosis due to the varying frequency response in the recording instrument. Our data based on the Sanborn crystal microphone[26] do not support this statement. The main criticism that one can make of their reports is the absence of surgical, necropsy or left heart catheterization data, which makes evaluation of the degree of severity extremely difficult. Our findings suggest that the estimation of the degree of severity is undoubtedly difficult to make on the basis of the t time and the ejection angle. Nevertheless, the total ejection time and the u time gave significant values and were accepted as reliable information. Additionally, significant change in the measurement after valvulotomy, accompanied by a reduction in the left ventricular-aortic pressure gradient and partial relief of the obstructive process, was observed (Fig. 17).

It has been suggested[25] that a prolonged total ejection time with delay in the u time can be found in patients with myocardial failure. The opposite phenomenon should, in fact, be expected, i.e., decrease of the total ejection time. Left heart failure of any cause, by decreasing the cardiac output and left ventricular stroke volume, tends to decrease the duration of left ventricular systole. Twenty consecutive cases of congestive failure due to ischemic heart disease were studied and these confirmed the presence of shortened total ejection time (Fig. 18).

The fact that a significant reduction in the left ventricular-aortic pressure gradient after valvulotomy was followed by a decrease in the total ejection time and u time suggests that the method may be helpful in evaluating the benefit obtained at surgery (Table II).

Mitral Stenosis: Systemic output, in the absence of valvular insufficiency, depends on the amount of blood that flows through the mitral valve. Rate of flow is related to pressure gradient across the valve. In mitral stenosis an increase in left atrial and pulmonary artery pressures is a protective mechanism sustaining adequate left ventricular filling. Thus, a circulatory equilibrium in mitral stenosis between changes in pressure and flow has to be established. Although wide ranges for pressure and flow are observed in mitral stenosis,

the final result is a pressure rise in the pulmonary circulation, a decrease in early left ventricular filling and a decrease of systemic output.[14,16,30] From the aforementioned, a small pulse wave and a decreased total left ventricular ejection time could be expected.[30] A comparison of the total ejection time in mitral stenosis with that of the normal condition revealed a reduction below the limits of normal when corrected for the heart rate. This difference, although not very striking, seems to be significant.

As with aortic stenosis, our patients represent moderate or severe degrees of mitral stenosis. The total ejection time may be normal in patients with mild or even moderate stenosis and a normal total ejection time does not exclude the presence of this lesion. The postoperative analysis revealed a tendency for the total ejection time to increase after valvulotomy (Fig. 7). The increase, although significant, was less than would have been expected.

We believe that this method is of value in the study of the hemodynamic abnormalities in patients with mitral stenosis and aortic stenosis. The simplicity, safety and reproducibility of the method make it a useful ancillary instrument in diagnosis and in the pre- and postoperative evaluation of these valvular lesions.

Summary and Conclusions

Indirect carotid artery tracings were studied in forty consecutive patients with mitral stenosis, twenty-five consecutive patients with aortic stenosis and thirty normal subjects. All abnormalities were proved by surgery or postmortem examination. Eighteen patients with mitral stenosis and seventeen patients with aortic stenosis were studied both pre- and postoperatively.

The indirect carotid tracing in patients with mitral stenosis revealed a short total ejection time. Cardiac catheterization was performed in ten patients; a tendency toward a short total ejection time was observed in patients with small stroke volume and decreased cardiac output. After mitral valvulotomy, the majority of patients presented increased total ejection time.

The group with aortic stenosis revealed a markedly abnormal carotid tracing. The total ejection time was above the limits of normal in all patients. The upstroke time was abnormal in 82 per cent of the patients. The ejection angle and the t time were abnormal in 72 per cent of patients, respectively. After aortic valvulotomy a decrease in total ejection time and upstroke time occurred in the majority of patients.

Two patients with proved subaortic stenosis (infundibular type) revealed an unusual carotid tracing characterized by a rapid upstroke time, normal t time and ejection angle, double systolic wave and marked prolongation of the total ejection time. One patient with membranous type revealed the same pattern as described for the valvular type of aortic stenosis.

The direct central aortic pressure tracing was analyzed in twenty patients with aortic stenosis. This revealed somewhat greater u time when compared with the indirect carotid tracing, but was otherwise identical.

From our observations, it is suggested that the analysis of the indirect carotid tracing is a simple and safe method which can give reliable information concerning the hemodynamics in aortic stenosis and mitral stenosis.

Acknowledgment

We wish to thank Drs. W. Woodward, E. Crow and J. Carson, Mrs. Natalie Razafsky and Mrs. Jo Ann Clifford for their technical assistance. The surgery was performed in all cases by Dr. C. Frederick Kittle.

Addendum

After the paper had been accepted for publication, two patients with rheumatic aortic valve stenosis (valvular type) were seen. Both presented significant findings in the carotid tracings. The preoperative tracings were typical of aortic valve stenosis but the postoperative tracings revealed a pattern similar to that found in the patients with *subaortic* stenosis. At operation they were found to have severe muscular hypertrophy of the outflow tract of the left ventricle. The pressure gradient and the total ejection time *increased* after aortic valvulotomy (Fig. 19).

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Pulmonic Stenosis

A Clinical Assessment of Severity*

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THE BEDSIDE diagnosis of pure pulmonic stenosis is usually an easy one in the majority of patients,[1–3] cardiac catheterization being performed mainly to determine the right ventricular systolic pressure and thereby assess the degree of valvular obstruction in anticipation of surgery. Thus, the problem arises in selecting patients for this preoperative procedure. It is under these circumstances and also in the re-evaluation of patients who have undergone surgery that the clinical assessment of the severity of pulmonic stenosis acquires practical importance.

The purpose of this paper is to evaluate and compare the various clinical means usually relied on for this assessment.

MATERIAL AND METHODS

Thirty-four patients were studied. The diagnosis of pulmonic stenosis with a normal aortic root was confirmed in all by cardiac catheterization. Patients with added anomalies were excluded. The stenosis was valvular in thirty-one and infundibular in three. The age range of the patients was from ten to forty-four years. There were twelve females and twenty-two males. They were arbitrarily divided into groups of mild stenosis (right ventricular systolic pressure up to 50 mm. Hg), moderate stenosis (right ventricular systolic pressure between 50 and 100 mm. Hg) and severe stenosis (right ventricular systolic pressure above 100 mm. Hg). According to this classification, there were eleven patients with mild, nine with moderate and fourteen with severe stenosis.

Phonocardiograms were recorded in thirty-two patients on a Sanborn Stetho-Cardiette using, in the majority, the logarithmic sound tracings inscribed synchronously with a carotid pulse tracing. Respiration was held in mid-inspiration. The dicrotic notch of the carotid pulse tracing was used to identify the components of a split second sound.

Vectorcardiograms were recorded in twenty-five patients with a Sanborn Vectorcardiograph, using the Grishman cube system of electrode attachment.[4] Forces directed forward, downward or to the left of the subject were regarded as positive. The vectorcardiographic loops were interrupted by time markings of 0.0025 second, producing a teardrop image whose thick portion pointed towards the direction of inscription. Special attention was given to the following vectorcardiographic features: (1) the direction of inscription in all planes; (2) the "long axis"[5] in all planes. In the horizontal plane, this was defined as the angle subtended by the maximal vector and the XX′ axis, this angle being positive if anteriorly and negative if posteriorly displaced (Fig. 1A). In the sagittal plane, it was defined as the angle subtended by the maximal vector and the YY′ axis, this angle being positive when anteriorly displaced and negative when posteriorly displaced (Fig. 1B). In the frontal plane, it was defined as the angle subtended by the maximal vector and the XX′ axis, this angle being zero degrees when the maximal vector coincided with, and +90 degrees when inferior and perpendicular to the horizontal line (Fig. 1C); (3) the posterior deviation of the T sÊ loop in the horizontal plane was measured as the angle subtended by the "V_1 axis" and the "T loop axis," this angle being zero degrees when the T loop axis coincided with, and positive when to the left of the V_1 axis (Fig. 1D); and (4) the QRS-T sÊ angle in all planes; this angle being positive when the T axis is anterior to the QRS axis in the horizontal or sagittal plane or to its right in the frontal plane and negative when the T axis is posterior to the QRS axis in the horizontal or sagittal plane or to its left in the frontal plane.

A twelve-lead electrocardiogram, teleoroentgenogram, orthogram and tomogram were available in all patients.

Cardiac catheterization was performed in the usual manner, in a fasting state, using a Sanborn Poly-Viso direct writing recorder and an electromanometer. The arbitrary zero level for all pressures was 5 cm. posterior to the angle of Louis with the patient in the supine position. Cardiac output was determined by the direct Fick principle. Blood oxygen contents

* From the Cardiopulmonary Laboratory, Beilinson Hospital, and the Sick Fund of the General Federation of Labour, Petah Tiqva, Israel.

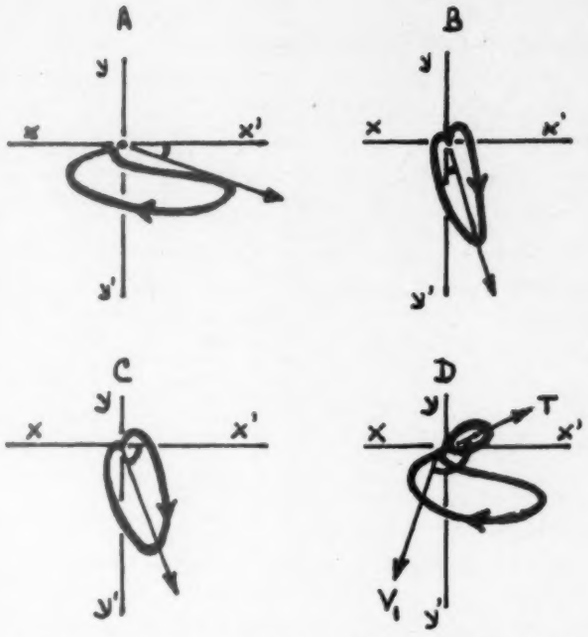

FIG. 1. A, long axis in the horizontal plane (angle subtended by the maximal vector and the XX′ axis in this plane). B, long axis in the sagittal plane (angle subtended by the maximal vector and the YY′ axis in this plane). C, long axis in the frontal plane (angle subtended by the maximal vector and the XX′ axis in this plane). D, posterior deviation of the T sÊ loop in the horizontal plane (angle subtended by the V_1 axis and the T loop axis in this plane). See text.

were measured with the Van Slyke manometric apparatus and oxygen consumption by expired air analysis with the Scholander apparatus.

RESULTS

The pertinent catheterization data are shown in Table I. They are tabulated in order of increasing right ventricular systolic pressure.

SYMPTOMS AND SIGNS

"Effort Incapacity" and Cyanosis: Some degree of palpitation and/or dyspnea was present in three of eleven patients with mild stenosis, five of nine with moderate stenosis and eleven of fourteen with severe stenosis. In all mild and most moderate cases, symptoms, when present, were mild and greatly relieved by reassurance alone, but above a right ventricular systolic pressure of 130 mm. Hg, effort incapacity was always evident. A rounded face, as described by Abrahams and Wood,[2] was seen in eight patients (23 per cent); it bore no relationship to the height of the right ventricular systolic pressure. Two patients with mild stenosis and three with moderate stenosis presented slight cyanosis on effort but in all except one, arterial oxygen saturation was normal, suggesting that the cyanosis was either of the peripheral type or due to redistribution of the systemic blood flow.[6] With a right ventricular systolic pressure of 120 mm. Hg or above, however, cyanosis was observed in six of seven patients together with arterial oxygen unsaturation and was probably the result of a reversed interatrial shunt.[7] A leaping jugular A wave, readily detectable on inspection, was never seen in patients with mild or moderate stenosis but it was present and confirmed by cardiac catheterization in nine of fourteen patients with severe stenosis; it was a constant finding with a right ventricular systolic pressure exceeding 130 mm. Hg.

Therefore, the conclusion may be drawn that the presence of clear-cut effort incapacity or cyanosis (especially if confirmed by arterial oxygen determinations) and/or leaping jugular A waves speaks strongly for high right ventricular systolic pressure (probably about 130 mm. Hg) and against mild or moderate stenosis (Table v).

Precordial bulging was present in one patient with mild stenosis, two with moderate stenosis and nine with severe stenosis. It was a constant finding with a right ventricular systolic pressure above 180 mm. Hg. *Right ventricular heaving*, when present, was best felt along the left sternal border in the second, third and fourth interspaces; it was never detected in patients with mild stenosis but was present in five of nine patients with moderate stenosis and in all patients with severe stenosis. Hence, its absence excludes severe stenosis.

A systolic thrill was felt in two of eleven patients with mild stenosis, three of nine patients with moderate stenosis and eleven of fourteen patients with severe stenosis. Its presence, therefore, favored severe stenosis, yet its intensity bore no relation to the right ventricular systolic pressure and was of little aid in assessing the severity of the stenosis.

For practical purposes, then, a strong right ventricular heaving suggests moderate or severe stenosis while a clear-cut precordial bulging points more specifically towards severe stenosis (Table v).

AUSCULTATION

Systolic Ejection Click: An "early systolic click"[8] was present in five of eleven patients with mild stenosis, three of nine with moderate stenosis but in only two of fourteen patients

TABLE I

Catheterization Data in Thirty-Four Patients with Pure Pulmonic Stenosis

Case No., Age (yr.) and Sex	Pulmonary Capillary Mean Pressure (mm. Hg)	Pulmonary Artery Pressure (mm. Hg)			Right Ventricular Pressure (mm. Hg)			Right Auricular Mean Pressure (mm. Hg)	Systemic Pressure (Intra-arterial) (mm. Hg)			Peripheral Oxygen Saturation (%)†	Type of Stenosis‡
		Systolic	Diastolic	Mean	Systolic	Diastolic	Mean		Systolic	Diastolic	Mean		
Patients with Mild Stenosis													
1, 38, F	3	15	4	6	33	2	10	1	110	70	80	96	V
2, 14, F	4	12	6	10	34	3	12	1	100	60	70	95	V
3, 12, F	5	17	5	13	35	3	13	3	115	70	90	98	V
4, 15, M	..	15	6	11	37	3	8	2	120	65	75	96	V
5, 26, M	10	17	4	12	37	4	8	3	140	80	100	97	V
6, 24, M	..	21	10	18	38	2	10*	..	130	70	90	95	V
7, 38, F	6	22	10	13	38	5	15	4	130	80	100	96	V
8, 30, M	7	20	13	18	38	8	14	4	120	80	90	97	V
9, 14, F	10	15	5	7	45	10	17	6	130	90	100	95	V
10, 34, F	7	22	8	14	45	6	14	4	120	70	90	96	V
11, 14, M	10	20	10	16	45	4	17	3	105	70	90	96	V
Patients with Moderate Stenosis													
12, 20, M	15	13	6	11	55	5	20	2	100	60	80	96	V
13, 13, M	9	13	7	10	62	5	22	3	100	70	90	96	V
14, 44, M	4	15	10	13	66	5	25	4	140	100	125	96	V
15, 10, M	..	18	8	10	75	1	25	1	120	70	80	96	V
16, 13, M	7	15	8	10	75	3	17	2	120	60	95	96	V
17, 12, M	..	21	12	16	78	8	30	6	105	60	90	97	I
18, 18, F	7	15	5	10	82	5	20	3	105	60	90	91*	V
19, 11, M	4	20	11	18	85	3	30	2	120	60	80	95	V
20, 14, M	7	21	4	10	85	2	25	4	120	80	100	95	V
Patients with Severe Stenosis													
21, 16, M	6	13	6	8	100	6	22	2	100	65	80	94	V
22, 26, F	6	24	5	12	100	5	12	4	120	70	90	94	V
23, 9, M	5	20	7	10	100	6	20	3	110	70	80	95	V
24, 14, F	..	14	6	10	100	6	21	2	85	60	70	88*	V
25, 10, M	5	20	10	15	105	6	45	3	82	48	62	93	I
26, 13, M	2	17	3	8	115	5	..	3	120	75	95	94	I
27, 20, M	..	20	3	10	115	10	30	..	100	55	95	93	V
28, 24, F	6	16	6	8	120	5	42	4	110	70	95	88*	V
29, 20, F	7	13	6	9	130	10	50	5	115	75	90	84*	V
30, 43, M	..	15	7	11	135	10	65	12	120	75	100	92*	V
31, 15, M	..	14	6	10	180	5	60	6	90	60	75	96	V
32, 29, M	15	..	15	..	190	8	80	10	135	82	92	92*	V
33, 10, M	8	15	9	12	195	6	50	5	130	70	90	91*	V
34, 22, F	6	17	7	10	200	5	100	5	90	42	58	92*	V

* Unsaturation, probably the result of reversed interatrial shunt.
† Lower limit of normal in this laboratory, 93 per cent.
‡ V = valvular; I = infundibular.

with severe stenosis (Table II). It was best heard along the left sternal border and on expiration in most patients. At times this gave the impression of an increased or duplicated first sound, the real nature of which was revealed by careful auscultation thoughout the respiratory cycle. Thus, the click, although most frequent in patients with mild stenosis, was by no means constant and was also heard twice in patients with severe stenosis (respective right ventricular systolic pressures 100 and 130 mm. Hg). It follows that neither its presence was pathognomonic for mild stenosis nor its absence distinctive for severe stenosis. Nevertheless, a systolic click was never heard in the five patients of this series whose right ventricular systolic pressure was above 130 mm. Hg, suggesting that its presence speaks strongly against a right ventricular systolic pressure of this magnitude.

Pulmonic Second Sound: The pulmonic component of the second sound was audible in all patients with mild stenosis and softer than usual in only three. In the patients with moder-

TABLE II
Comparison Between Phonocardiographic and Auscultatory Findings

Case No.	Right Ventricular Pressure (mm. Hg)	Early Systolic Click		Peak of Systolic Murmur*		Pulmonic Closure (intensity)†		Increased Fourth Sound		Aorto-pulmonic Interval (sec.)
		Phono-cardio-gram	Aus-culta-tion	Phono-cardio-gram	Aus-culta-tion	Phono-cardio-gram	Aus-culta-tion	Phono-cardio-gram	Aus-culta-tion	
				Patients with Mild Stenosis						
2	34/3	+	+	E	E	N	N	−	−	0.04
3	35/3	−	−	E	E	N	N	−	−	0.05
5	37/4	+	+	E	E	N	S	−	−	0.06
6	38/2	+	+	E	E	N	S	−	−	0.06
7	38/5	+	+	E	E	N	S	−	−	0.05
8	38/8	−	−	E	E	N	N	−	−	0.06
9	45/10	−	−	E	E	N	N	−	−	0.05
10	45/6	+	+	E	E	N	N	−	−	0.06
11	45/4	−	−	M	E	N	N	−	−	0.05
				Patients with Moderate Stenosis						
12	55/5	−	−	E	E	Sm	N	−	−	0.07
13	62/5	−	−	E	E	Sm	S	−	−	0.05
14	66/5	+	+	M	E	Sm	S	−	−	0.07
15	75/1	+	+	M	E	Sm	S	−	−	0.07
16	75/3	−	−	M	E	Sm	N	−	−	0.05
17	78/8	+	+	L	L	Sm	S	−	−	0.08
18	82/5	−	−	L	E	V. Sm	S	−	−	0.10
19	85/3	−	−	M	L	V. Sm	S	−	−	0.07
20	85/2	−	−	L	L	V. Sm	S	−	−	0.08
				Patients with Severe Stenosis						
21	100/6	−	−	L	L	V. Sm	S	−	−	0.08
22	100/5	−	−	L	L	V. Sm	S	−	−	0.11
23	100/6	−	−	L	E	V. Sm	S	+	−	0.08
24	100/6	+	+	E	E	Sm	S	−	−	0.06
25	105/6	−	−	L	L	Sm	S	−	−	0.08
26	115/50	−	−	M	E	Abs	S	−	−	...
27	115/10	−	−	L	L	Sm	S	+	−	0.12
28	120/5	−	−	L	E	Abs	S	+	+	...
29	130/10	+	+	L	L	V. Sm	S	−	−	0.12
30	135/10	−	−	L	L	Abs	S	+	+	...
31	180/5	−	−	L	L	V. Sm	S	−	−	0.10
32	190/8	−	−	L	L	V. Sm	S	+	+	0.14
33	195/8	−	−	L	L	V. Sm	S	+	+	0.12
34	200/5	−	−	L	L	V. Sm	S	+	+	0.12

* E = early; M = mid; L = late.
† N = normal; Sm = small; V. Sm = very small; Abs = absent; S = soft or undetectable.

ate stenosis, it was delayed but of normal intensity in two, soft and delayed in four and undetectable in three. It was audible in only two patients with severe stenosis and in both was very soft and delayed. This is in accordance with previous investigations.[9-11] It can be stated that a split second sound with clear pulmonary closure denotes mild stenosis; wider splitting with soft pulmonary closure denotes moderate stenosis and absence of pulmonary closure denotes severe stenosis.

Atrial Sound: A fourth heart sound, probably

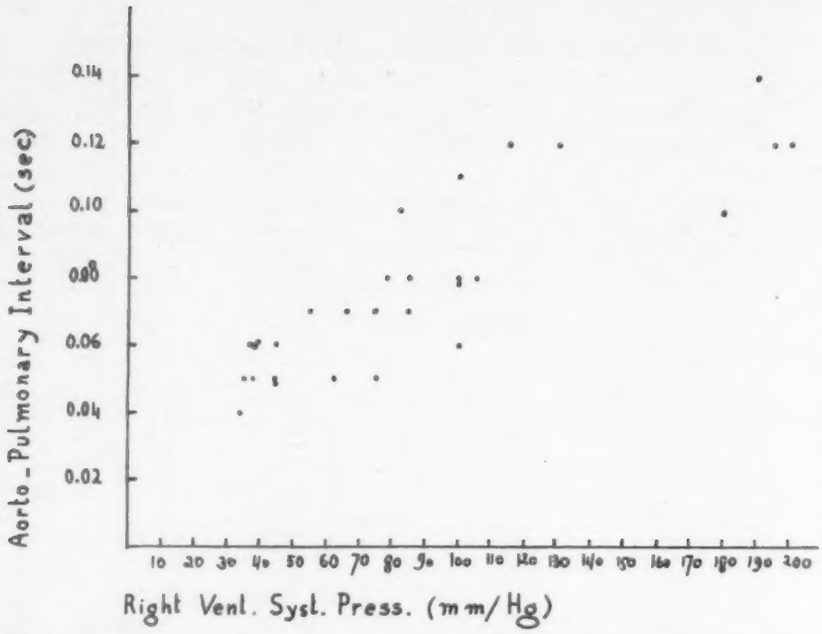

FIG. 2. Correlation between the aortopulmonary interval and the right ventricular systolic pressure. See text.

the result of forceful right atrial contraction, was never heard in patients with mild or moderate stenosis in this series. Although its appearance has been reported with a right ventricular systolic pressure of about 90 mm. Hg,[12] it appeared in our series only with a right ventricular systolic pressure of 120 mm. Hg and was heard in five of seven patients with pressures above this level. It was present in all three patients with a right ventricular systolic pressure above 180 mm. Hg.

Systolic Ejection Murmur: The systolic murmur was of the characteristic crescendo-decrescendo type (ejection murmur[13]) in all patients. Its intensity varied from grade 2 to grade 4 (graded 1 to 4) but there was no clear-cut relation between this intensity and the severity of the stenosis, some of the harshest murmurs occurring in patients with mild stenosis, and vice versa. Special attention was paid to locating the crest of the murmur in the systolic interval. Although this is difficult by auscultation alone, it could be determined in most patients whether this crest was "early" or "late": with an early crest, the decrescendo phase of the murmur was well heard; if late, the murmur started slightly later and had a harsh crescendo quality, its decrescendo phase often being "masked" to the ear. In this series the systolic peak was early in all of the patients with mild stenosis, in six of nine with moderate stenosis and in only four of fourteen with severe stenosis. Above a right ventricular systolic pressure of 130 mm. Hg, it was always clearly late. This is in accordance with previous reports[9,11] and it can be stated that a "late" systolic murmur excludes mild stenosis, whereas an "early" one is unusual in severe stenosis. These auscultatory findings are in good general agreement with the phonocardiographic results (*vide infra*).

PHONOCARDIOGRAMS

Systolic Ejection Click and Murmur: Nine patients with mild stenosis, nine with moderate stenosis, and fourteen with severe stenosis were studied (Table II). The early systolic click was confirmed in all five patients with mild stenosis, three with moderate stenosis and two patients with severe stenosis in whom it was originally disclosed by auscultation. The ejection type systolic murmur started slightly after the first sound or after the click when present. With two exceptions in moderate stenosis and two in severe stenosis, it extended beyond the aortic closure whenever the right ventricular systolic pressure clearly exceeded the systemic pressure; it ended before the pulmonic closure in all patients.

The peak of the murmur was reached progressively later with increasing right ventricular systolic pressures and was tabulated as "early," "mid" or "late" according to its early, mid or late position in the right ventricular systolic interval (the distance between the first sound

TABLE III
Electrocardiographic Findings in Thirty-Four Patients with Pure Pulmonic Stenosis

Case No.	Right Ventricular Pressure (mm. Hg)	Electrical Axis (degrees)	P in Lead II (mm.)	P-R Interval (sec.)	aVL (type)	aVR		aVF		Right Ventricular Activation Time	RV_4R	RV_1	RV_6	SV_1	SV_6	RV_1 / SV_6	T Wave Polarity in Precordial Leads
						Type	R (mm.)	Type	S (mm.)								
Patients with Mild Stenosis																	
1	33/2	+30	1.5	0.18	qR	rSr′	1.0	Rs	2.5	0.02	0.0	2.0	7.0	9.0	0.5	2.5	$+V_1$
2	34/3	+60	1.5	0.16	rS	qR	2.0	R	0.0	0.03	3.0	5.0	16.0	5.0	1.0	6.0	$+V_1$
3	35/3	+53	1.0	0.16	rS	rSr′	2.5	Rs	1.5	0.02	8.0	15.0	11.0	7.0†	4.0	19.0	$-V_1$
4	37/3	+75	1.0	0.16	rS	rSr′	3.0	Rs	3.0	0.03	3.5	7.5	5.5	7.0†	4.5	12.0	$+V_1$
5	37/4	+30	1.0	0.16	qR	qR	1.5	RS	3.0	0.02	2.0	2.0	11.0	6.0	1.0	3.0	$+V_1$
6	38/2	+105	1.0	0.16	rS	Qr	4.0	Rs	4.0	0.05	2.0	3.0	8.0	3.0†	5.0	8.0	$+V_1$
7	38/5	+28	2.0	0.20	qR	rSr′	1.0	Rs	2.0	0.02	4.0	6.5	13.0	10.0	0.5	7.0	$+V_1$
8	38/8	+103	1.5	0.20	rS	QR	5.0	RS	2.0	0.02	8.0	5.0	15.0	5.0†	9.0	14.0	$+V_1$
9	45/10	+74	1.0	0.14	rS	rSr′	1.5	qR	..	0.02	1.0	4.0	16.0	14.0	1.0	5.0	$-V_1$
10	45/6	+40	1.0	0.14	qR	Qr	1.0	Rs	1.0	0.02	0.5	2.0	8.5	10.0	0.5	2.5	$+V_1$
11	45/4	−4	1.5	0.14	qRs	qR	3.5	RsR′s′	..	0.05	3.0	8.0	12.0	3.0†	3.0	11.0	$+V_1$
Patients with Moderate Stenosis																	
12	55/5	+82	1.0	0.12	qRs	Qr	4.0	Rs	1.5	0.02	4.0	2.5	11.0	4.0	4.0	6.5	$+V_1$
13	62/5	+100	1.0	0.12	rS	qR	3.0	qR	..	0.04	10.0	14.0	7.0	4.0†	3.5	17.5	$-V_1$
14	66/5	+90	1.5	0.18	RS	QR	6.0	rS	4.0	0.035	1.0	1.0	5.0	2.5	7.0	8.0	$+V_1$
15	75/1	+92	2.0	0.14	qRS	rSR′	5.0	Rr′	..	0.02	12.0	12.0	12.0	3.0†	3.0	15.0	$-V_1$
16	75/3	+107	1.0	0.14	rS	rSr′	4.0	Rs	2.0	0.03	5.0	7.0	5.0	5.5†	1.5	8.5	$+V_1$
17	78/8	+112	1.0	0.12	rsr′	rSr′	12.0	qRS	8.0	0.05	13.0	23.0	12.0	3.0†	8.0	31.0	$-V_1$
18	82/5	+148	1.0	0.14	qRs	QR	4.5	rS	5.5	0.03	3.5	9.0	4.5	0.0†	3.0	12.0	$-V_1$
19	85/3	+98	2.5	0.18	rS	qR	6.0	qRs	2.0	0.02	15.0	17.0	23.0	4.5†	9.0	26.0	$+V_1$
20	85/2	+100	2.5	0.14	rS	qR	3.5	qRs	2.0	0.06	7.0	10.0	6.5	5.0†	3.0	13.0	$+V_1$
Patients with Severe Stenosis																	
21	100/6	+30	1.0	0.18	qRs	qR	5.5	rS	7.0	0.04	7.5	9.0	11.0	0.0	4.0	13.0	$+V_1$
22	100/5	+92	0.5	0.14	RS	qR	3.5	rsR′	..	0.03	12.0	17.0	7.0	10.0†	3.0	20.0	$+V_1$
23	100/6	+115	2.5	0.16	rS	QR	6.0	R	..	0.035	20.0	10.0	16.0	20.0	8.0	18.0	$+V_1$
24	100/6	+108	2.0	0.14	rS	Qr	0.5	qR	..	0.04	5.0	2.0	6.0	4.0	4.5	6.5	$-V_1$
25	105/6	+112	1.5	0.18	rS	Qr	2.5	qR	..	0.04	8.0	9.0	12.0	0.5†	5.0	14.0	$-V_4$
26	115/5	+115	2.5	0.14	rS	rSr′	4.0	qRs	0.5	0.04	22.0	17.0	12.0	25.0	5.5	23.0	$-V_2$
27	115/10	+153	2.5	0.16	rS	qR	8.0	RS	7.5	0.04	19.0	11.0	7.0	0.0†	6.5	18.0	$-V_1$
28	120/5	+110	1.5	0.14	rS	qR	4.0	R	0.0	0.04	14.0	21.0	4.0	7.0†	1.5	23.0	$-V_1$
29	130/10	+158	1.0	0.16	rS	qR	7.0	qR	0.0	0.05	11.0	20.0	2.5	0.0†	5.5	27.0	$-V_4$
30	135/10	+114	3.0	0.18	rS	Qr	1.5	qR	0.0	0.04	4.5	5.0	10.0	0.0†	8.0	13.0	$-V_4$
31	180/5	+135	3.0	0.16	rS	qR	9.5	qRs	0.5	0.06	..	29.0	3.0	1.5†	20.0	49.0	$-V_4$
32	190/8	+133	3.5*	0.25	QS	qR	4.5	Rs	0.5	0.04	7.5	10.0	4.0	0.0†	14.0	24.0	$-V_4$
33	195/6	+120	3.5*	0.22	rS	qR	12.0	qRs	3.5	0.06	30.0	28.0	6.0	0.0†	8.0	36.0	$-V_5$
34	200/5	+143	3.0*	0.20	rS	QR	9.0	qRs	0.5	0.04	..	12.0	6.0	0.0†	5.0	17.0	$-V_4$

* PV_1 = 5 mm.
† $R/SV_1 > 1$.

and the pulmonic closure). Eight patients with mild stenosis showed an early and one a mid peak; two patients with moderate stenosis showed an early, four a mid and three a late peak; one patient with severe stenosis showed an early, one a mid peak and twelve a late peak. A late peak, therefore, practically excludes mild stenosis and speaks strongly against moderate stenosis while an early peak speaks against severe stenosis.

Pulmonic Second Sound: The pulmonic component of the second sound (pulmonic closure) was of normal size in all patients with mild stenosis, clearly smaller than the aortic closure in patients with moderate stenosis and barely discernible in patients with most severe stenosis (Table II). The distance between aortic and pulmonic closures varied between 0.04 and 0.06 second in mild stenosis, 0.05 and 0.10 second in moderate stenosis, and between 0.06 and 0.14 second in severe stenosis. This distance was, therefore, wider than normal in all patients (normal = 0.01 to 0.03 second in mid-inspiration) and when plotted against the right ventricular systolic pressure revealed a good linear relation. Figure 2, based on the findings

TABLE IV
Vectorcardiographic Findings in Twenty-Five Patients with Pure Pulmonic Stenosis

Case No.	Right Ventricular Pressure (mm. Hg)	Horizontal Plane				Sagittal Plane			Frontal Plane		
		Direction of Inscription*	"Long Axis" (degrees)	QRS-T sÊ Angle (degrees)	Posterior Deviation of T (degrees)	Direction of Inscription*	"Long Axis" (degrees)	QRS-T sÊ Angle (degrees)	Direction of Inscription*	"Long Axis" (degrees)	QRS-T sÊ Angle (degrees)
Patients with Mild Stenosis											
2	34/3	CCW/CW	+70	±0	+70	CCW	+6	±0	CW	+60	±0
3	35/3	CW	+7	−15	+95	CCW	+6	+10	CW	+70	−10
5	37/4	CCW	+2	+43	+60	CW	+4	−15	CCW/CW	+55	+20
6	38/2	CW	+12	+40	+70	CW/CCW	+7	−7	CCW/CW	+60	+18
7	38/5	CCW	+5	±0	+85	CCW	+8	+2	CCW/CW	+58	±0
9	45/10	CCW	+5	+42	+75	CW	+4	−10	CCW/CW	+75	+5
11	45/4	CW	+15	±0	+90	CCW	+5	±0	CW	+70	±0
Patients with Moderate Stenosis											
12	55/5	CW	+10	+10	+75	CCW	+6	−9	CW	+60	+12
13	62/5	CW	+60	−120	+110	CW	+10	+35	CW	+90	−25
15	75/1	CW	+21	−28	+105	CCW	+13	+19	CW	+70	+5
17	78/8	CW	+58	−90	+122	CCW	+12	−15	CW	+85	−30
18	82/5	CW	+30	−18	+95	CCW	+13	+12	CW	+72	−5
19	85/3	CW	+32	−40	+110	CCW	+12	+10	CW	+75	+3
20	85/2	CW	+56	−10	+75	CW	+20	+5	CW	+75	−5
Patients with Severe Stenosis											
21	100/6	CW	+41	−10	+80	CCW	+12	−10	CW	+82	−5
22	100/5	CW	+28	−120	+110	CCW	+18	+10	CW	+130	±0
23	100/6	CW	+26	−8	+90	CW/CCW	+20	+8	CW	+85	−8
24	100/6	CW	+28	−10	+120	CW	+22	+5	CW	+85	+3
25	105/6	CW	+35	−117	+110	CW/CCW	+18	+15	CW	+90	−12
26	115/5	CW	+46	−60	+122	CW	+20	+5	CW	+95	−22
27	115/10	CW	+60	−18	+140	CCW	+30	+16	CW	+85	−105
28	120/5	CW	+53	−120	+120	CW/CCW	+25	+180	CCW/CW	+70	−18
29	130/10	CW	+32	−180	+125	CW	+16	−0	CW	+82	−120
32	190/8	CW	+22	−60	+140	CW	+20	±0	CW	+62	−140
33	195/6	CW	+75	−180	+170	CCW	+33	±0	CW	+110	−180

* CCW = counterclockwise; CW = clockwise.

in the twenty-nine patients in whom the aortopulmonic interval could be measured accurately, clearly shows this relation. This illustration also shows that despite some degree of overlapping, an interval of 0.07 second or more practically excludes mild stenosis and one of 0.11 second or more excludes both mild and moderate stenosis.

Atrial Sound: A prominent fourth heart sound was recorded in the five patients in whom it was originally disclosed by auscultation and in two additional patients with right ventricular systolic pressures of 100 and 115 mm. Hg, respectively. It was never prominent in mild or moderate stenosis (Table II). The phonocardiographic findings are in agreement with previous investigations.[8,9,14]

ELECTROCARDIOGRAMS

Electrical Axis: A twelve-lead electrocardiogram was available in all thirty-four patients (Table III). All patients had sinus rhythm. The electrical axis ranged between −4 and +105 degrees in mild stenosis, between +82 and +148 degrees in moderate stenosis and between +30 and +158 degrees in severe stenosis. With increasing right ventricular systolic pressure, the axis tended to deviate towards the right, but considerable overlapping was present. No satisfactory linear relation was obtained by plotting these values against each other, the only point derived being that an electrical axis to the right of +100 degrees is unusual in mild stenosis.

Clockwise rotation (Qr or QR pattern in lead aVR and/or Rs pattern extending to leads V_5 and V_6) was present in six patients with mild stenosis, six patients with moderate stenosis and thirteen patients with severe stenosis. No linear relation was obtained by plotting the height of R in lead aVR against the right ventricular systolic pressure.

P Waves: Pulmonary P waves (pointed P waves taller than 3 mm. in lead II and/or lead V_1) were never seen with a right ventricular systolic pressure below 130 mm. Hg. They were present in five patients with a right ventricular systolic pressure above this level, with the tallest P (P in lead V_1 = 5 mm.) recorded in three patients with right ventricular systolic pressures of 190, 195 and 200 mm. Hg, respectively. The P-R interval was normal in all except in two patients with very severe stenosis (respective right ventricular systolic pressures 190 and 195 mm. Hg; and P-R intervals 0.25 and 0.22 second). A tall and peaked P wave and/or a prolonged P-R interval are, therefore, late signs. When present, however, they invariably indicate severe stenosis, as has been previously reported.[2,3]

Precordial Leads: The height of R in the right precordial lead with maximal R wave (referred to henceforth as RV_1 for simplification) varied between zero and 15 mm. in patients with mild stenosis, between 1 and 23 mm. in patients with moderate stenosis and between 5 and 29 mm. in patients with severe stenosis (Table III). When plotted against the right ventricular systolic pressure, no convincing linear relation was obtained and the right ventricular systolic pressure could not be predicted from the height of R in the right precordial leads. It was noted only that an R taller than 5 mm. in these leads spoke against mild stenosis and an R taller than 23 mm., against both mild and moderate stenosis.

$RV_1 + SV_6$ was between 2.5 and 19 mm. in mild stenosis, between 6.5 and 31 mm. in moderate stenosis and between 6.5 and 49 mm. in severe stenosis. Considerable overlapping was again present and no definite linear relation was obtained by plotting this value against the right ventricular systolic pressure.

Inverted T waves beyond lead V_1 were not observed in mild or moderate stenosis; they were inverted through lead V_2 in two patients with severe stenosis whose right ventricular systolic pressure was less than 130 mm. Hg; above this level, they were inverted through lead V_4 in all. Inversion of the T wave beyond lead V_1 suggests, therefore, severe stenosis and inversion through lead V_4, a right ventricular systolic pressure above 130 mm. Hg.

VECTORCARDIOGRAMS

Vectorcardiographic records were available in seven patients with mild stenosis, seven patients with moderate stenosis and eleven patients with severe stenosis (Table IV).

Horizontal Plane: In patients with mild stenosis, the direction of inscription of the QRS loop was normal (counterclockwise) in three, typical for right ventricular hypertrophy (short counterclockwise followed by large clockwise inscription) in three, and of a figure-of-eight pattern in one. All patients with moderate and severe stenosis showed a typical pattern of right ventricular hypertrophy. Therefore, a normal direction of inscription in this plane excludes both moderate and severe stenosis. With increasing right ventricular systolic pressures, the body of the loop as a whole tended to deviate progressively to the right, as reflected by the progressive increase of the angle of the long axis. Yet the relation obtained by plotting this angle against the right ventricular systolic pressure was not linear enough to make it of practical value (Fig. 3A). Similarily, no clear-cut linear relation was obtained by plotting the QRS-T s$\hat{E}$ angle against the right ventricular systolic pressure.

The best linear relation in this plane was obtained by plotting the posterior deviation of the T loop against the right ventricular systolic pressure (Fig. 3B). It may be seen that a posterior deviation of T greater than 95 degrees excludes mild stenosis and one greater than 122 degrees excludes both mild and moderate stenosis.

Sagittal Plane: The direction of inscription of the QRS loop followed no set pattern in any of the groups. With increasing right ventricular systolic pressure, the long axis tended to deviate progressively forward, and a good linear relation was obtained by plotting these values against each other (Fig. 3C). It can be seen that a forward deviation greater than 8 degrees speaks against mild stenosis and one greater than 20 degrees against both mild and moderate stenosis. No clear-cut linear relation was obtained by plotting the QRS-T s$\hat{E}$ angle in this plane against the right ventricular systolic pressure.

Frontal Plane: In patients with mild stenosis, a clear-cut figure-of-eight pattern (large counterclockwise inscription followed by clockwise inscription) was seen in four patients and a clockwise inscription in three. In moderate and severe stenosis, the inscription was always clockwise, sometimes preceded by a tiny counterclockwise inscription. Therefore, in this plane, a clear-cut figure-of-eight pattern

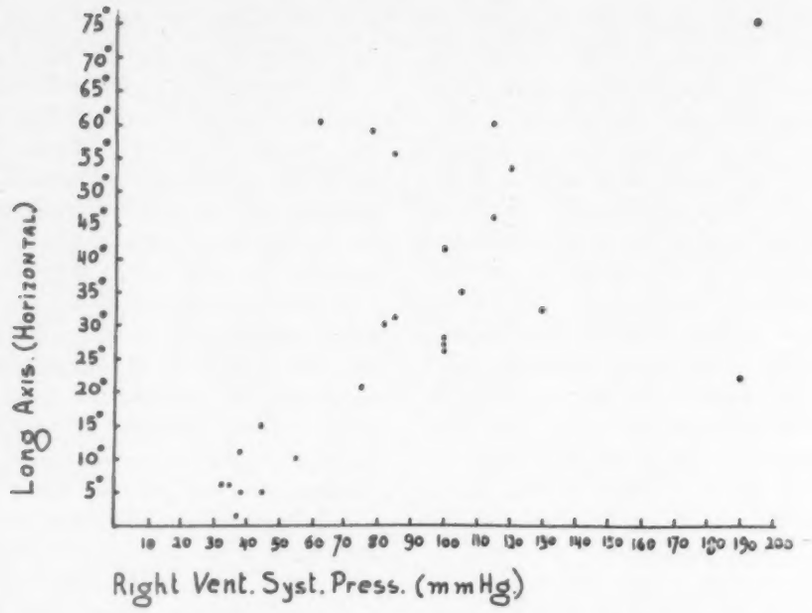

FIG. 3A. Correlation between the angle of the long axis in the horizontal plane and the right ventricular systolic pressure.

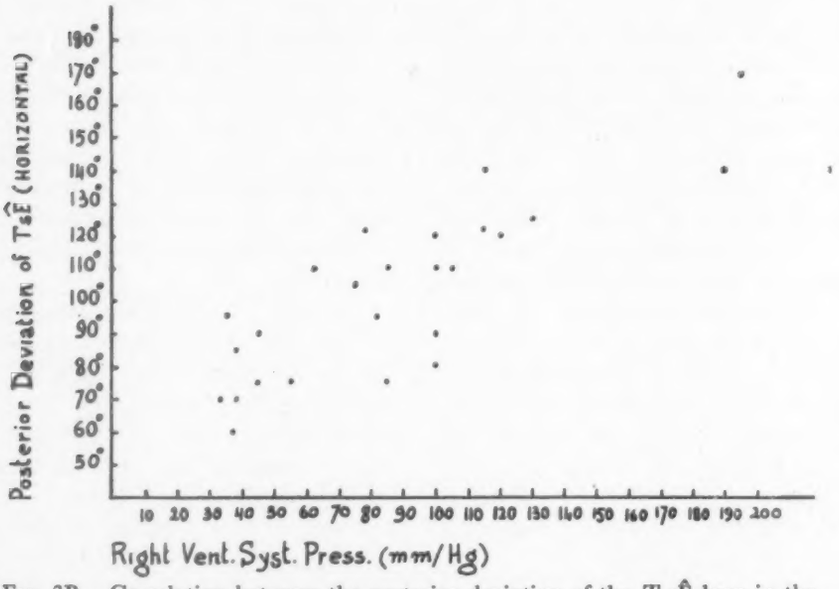

FIG. 3B. Correlation between the posterior deviation of the T sÊ loop in the horizontal plane and the right ventricular systolic pressure.

speaks against moderate and severe stenosis.

With increasing right ventricular systolic pressure, the long axis tended to deviate progressively towards the right, but no convincing linear relation could be obtained by plotting these values against each other (Fig. 3D). No clear-cut linear relation was obtained by plotting the QRS-T sÊ angle in this plane against the right ventricular systolic pressure.

None of the loops showed evidence of conduction delay in any of the planes.

The vectorcardiographic observations reported here are in accordance with previous reports on the changing vectorcardiographic pattern encountered with progressive increase of the right ventricular systolic pressure.[15,16] Six typical examples are seen in Figure 4.

TELEOROENTGENOGRAMS

X-ray examinations of the chest were available in all thirty-four patients.

The cardiothoracic ratio varied between 36

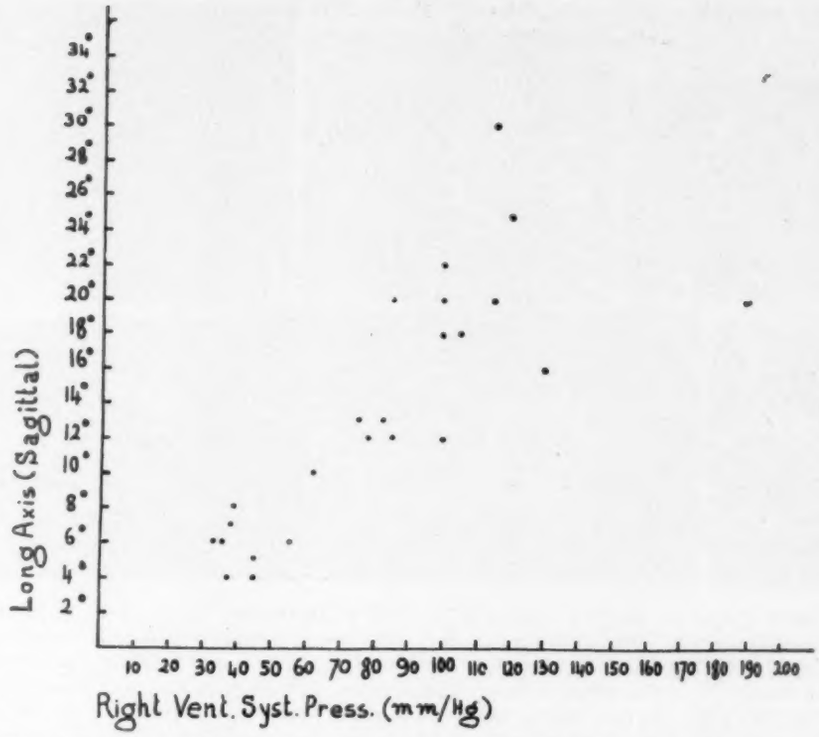

FIG. 3C. Correlation between the angle of the long axis in the sagittal plane and the right ventricular systolic pressure.

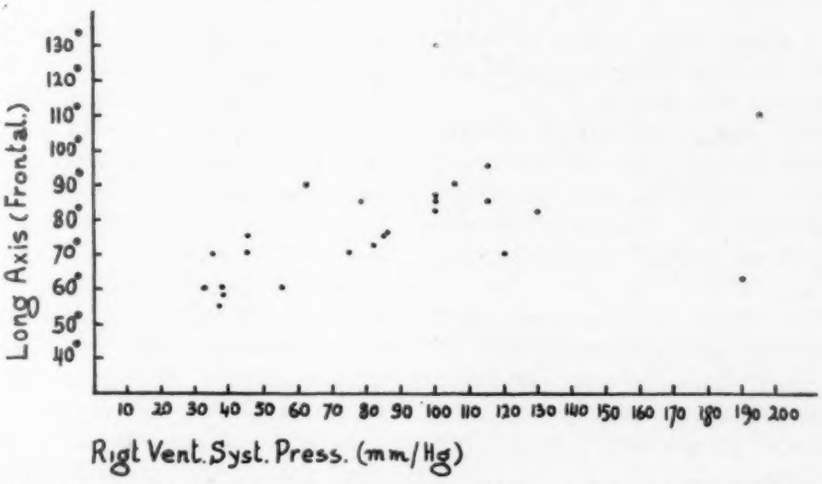

FIG. 3D. Correlation between the angle of the long axis in the frontal plane and the right ventricular systolic pressure.

and 46 per cent in mild stenosis, between 39 and 47 per cent in moderate stenosis and between 41 and 62 per cent in severe stenosis. No linear relation could be detected between the cardiothoracic ratio and the severity of the stenosis, but with a right ventricular systolic pressure above 130 mm. Hg (six patients) this ratio was always above 50 per cent. That an increased cardiothoracic ratio is found mainly in severe stenosis has been previously reported.[2,3]

A poststenotic dilatation of the pulmonary artery was present in all patients except two with mild stenosis, two with moderate stenosis and six with severe stenosis despite a withdrawal curve showing signs of pure valvular stenosis in these exceptional cases. No direct relation was detected between the degree of poststenotic dilatation and the severity of the stenosis. It is worth emphasizing that some of the largest poststenotic dilatations were seen in patients with

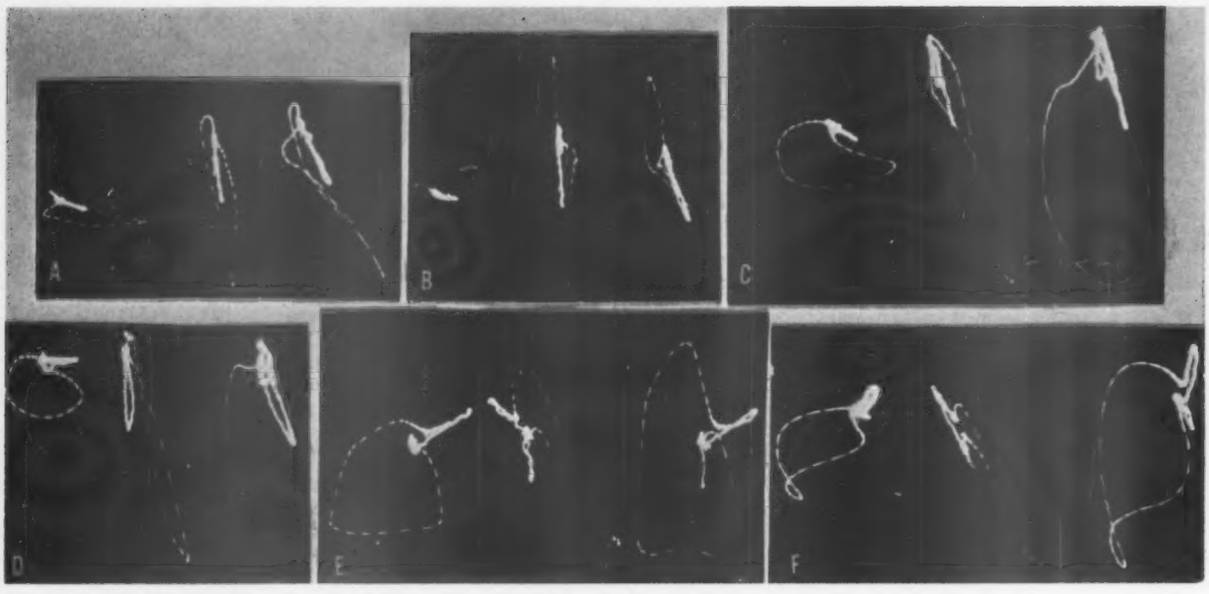

FIG. 4. Vectorcardiograms of six patients arranged in order of increasing right ventricular systolic pressure. A, Case 7: right ventricular systolic pressure 38/5 mm. Hg. B, Case 11: right ventricular systolic pressure 45/4 mm. Hg. C, Case 23: right ventricular systolic pressure 100/6 mm. Hg. D, Case 25: right ventricular systolic pressure 105/6 mm. Hg. E, Case 27: right ventricular systolic pressure 115/10 mm. Hg. F, Case 33: right ventricular systolic pressure 195/6 mm. Hg. In each picture from left to right, horizontal, sagittal and frontal plane loops. With increasing right ventricular systolic pressure there is a progressive deviation of the QRS sÊ loop to the right as seen in the horizontal and frontal loops, and anteriorly as seen in the sagittal and horizontal loops. The progressive increase in the posterior deviation of the T sÊ loop is also well seen.

milder stenosis, a point which deserves further study. The hilar vascular pattern tapered off in a normal fashion in all patients.

With increasing right ventricular systolic pressure, the right lower arch of the heart showed progressive bulging but this could not be measured and correlated objectively because of different degrees of rotation of the postero-anterior film.

The impression gained by reviewing these findings was that the teleoroentgenograms of the chest helped especially in the rapid detection of the most severe cases, but that they contributed little otherwise in assessing the severity of pulmonic stenosis.

The tomographic findings will be reported in detail in a subsequent paper.

COMMENTS

In comparing the different results, the phonocardiogram stood out as very reliable and probably as the method of choice in assessing the severity of pulmonic stenosis. Indeed, the fourth heart sound, the early systolic click, the characteristics of the systolic murmur and of the pulmonic closure and, especially, the magnitude of the aortopulmonic interval, constituted an array of highly reliable reference points. It can, for instance, be seen by comparing the different relations shown in Figures 2 and 3 that the aortopulmonic interval proved itself to be at least as good a gauge of the right ventricular systolic pressure as any of the vectorcardiographic features.

In accordance with previous investigations,[15–17] analysis of the vectorcardiographic data conveyed the impression that they reflected the right ventricular burden somewhat more reliably than the electrocardiographic manifestations. Moreover, a review of the electrocardiographic results revealed a less convincing linear relation to the right ventricular systolic pressure than some recent reports would indicate,[18,19] a discrepancy which may be possibly explained by the difference in the average age groups of the patients studied. As for the teleoroentgenographic findings, it has already been stressed that their contribution to the assessment of the severity of pulmonic stenosis was limited.

Finally, an attempt was made to compare the main phonocardiographic and auscultatory results (Table II). Correlation was very good as far as the early systolic click was concerned and almost as good for the fourth heart sound. In locating the peak of the murmur in the sys-

tolic cycle by auscultation, correlation was very good in patients with mild stenosis (one error), good in patients with severe stenosis (three errors) and poor in patients with moderate stenosis (five errors), auscultation being in error mainly by locating a peak as early while it appeared late in the phonocardiogram. Altogether, auscultation was in error, therefore, in nine of thirty-two trials (28 per cent). In assessing the intensity of the pulmonic closure, auscultation was in error three times in patients with mild stenosis, twice in patients

TABLE V
Main Reference Points for the Assessment of the Right Ventricular Systolic Pressure

	Mild Pulmonic Stenosis	Moderate Pulmonic Stenosis	Severe Pulmonic Stenosis		
	Right Ventricular Systolic Pressure (mm. Hg)				
	<50	Between 50 and 100	100 to 130	130 to 180	>180
Signs and Symptoms					
Palpitation and dyspnea	−	±	+	++	++
Cyanosis (with arterial oxygen unsaturation)	−	−	±	+	+
Prominent jugular A waves	−	−	±	+	+
Precordial bulging	−	−	±	±	+
Right ventricular heave	−	±	+	+	++
Early systolic click	+	±	±	−	−
Pulmonic closure Intensity	N	S	VS or M	M	M
Delay	−	+	++	..	..
Fourth heart sound	−	−	−	+	+
Peak of systolic murmur (early [E] or late [L])	E	E or L	L	L	L
Phonocardiogram					
End of systolic murmur (overrides aortic closure)	−	±	†	†	†
Peak of systolic murmur (early [E], mid [M] or late [L])	E	M or L	L	L	L
Aortopulmonary interval (sec.)	0.04 to 0.06	0.05 to 0.10	0.06 to 0.14		
Electrocardiogram					
Electrical axis, range (degrees)	−4 to +105	+82 to +148	+30 to +158		
Pulmonary P*	−	−	−	+	+
Prolonged P-R interval	−	−	−	±	+
RV_1 range (mm.)	0 to 15	1 to 23	7 to 29		
T inverted beyond lead V_1	−	−	±	+	+

Continued

TABLE V (*Continued*)
Main Reference Points for the Assessment of the Right Ventricular Systolic Pressure

	Mild Pulmonic Stenosis	Moderate Pulmonic Stenosis	Severe Pulmonic Stenosis		
	Right Ventricular Systolic Pressure (mm. Hg)				
	<50	Between 50 and 100	100 to 130	130 to 180	>180
Vectorcardiogram					
Horizontal plane Direction of inscription	CCW or CW	CW	CW	CW	CW
Posterior deviation of T (degrees)	+60 to +90	+75 to +122	+80 to +170		
Saggital plane, long axis (degrees)	+4 to +8	+6 to +20	+12 to +33		
Frontal plane, direction of inscription	Figure-of-eight or CW	CW	CW	CW	CW
Roentgenograms					
Cardiothoracic ratio, range (%)	36 to 46	39 to 47	41 to 62		

NOTE: N = normal; S = soft; VS = very soft; M = missing; CCW = counterclockwise; CW = clockwise.
* Pointed P waves taller than 3 mm. in leads II and/or V_1.
† Overriding whenever right ventricular systolic pressure exceeds systemic systolic pressure.

with moderate stenosis and never in patients with severe stenosis. The over-all results suggest that most of the phonocardiographic findings could be arrived at by auscultation alone as the errors mainly involved the location of the peak of the systolic murmur in moderate stenosis.

The major points of reference used in predicting right ventricular systolic pressure are shown in Table V. They tend to accentuate the 100 mm. Hg landmark, the level around which many authors place the indications for surgery in pulmonic stenosis. Using these criteria, and often by auscultation or phonocardiography alone, it should be possible to readily select the potential candidate for surgery and thus the one in greatest need of further intensive study.

SUMMARY

The clinical, phonocardiographic, electrocardiographic, vectorcardiographic and teleoroentgenographic findings in thirty-four patients with proved pulmonic stenosis with a normal aortic root are analyzed and points of reference enabling assessment of the severity of the stenosis are presented and tabulated.

Patients with mild stenosis (right ventricular systolic pressure below 50 mm. Hg) present no effort incapacity. Characteristic findings include an early systolic click, an early peak of the systolic murmur, a normal pulmonic closure and an aortopulmonic interval between 0.04 and 0.06 second. The height of R in lead V_1 does not exceed 15 mm. The vectorcardiogram shows either clockwise or counterclockwise direction of inscription of the QRS loop in the horizontal plane and a posterior deviation of T between +60 and +90 degrees in this plane. The cardiothoracic ratio is normal.

Patients with moderate stenosis (right ventricular systolic pressure between 50 and 100 mm. Hg) show little effort incapacity if any, and have a soft and delayed pulmonic closure (aortopulmonic interval between 0.05 and 0.10 second); the height of R in lead V_1 does not exceed 23 mm.; the direction of inscription of the QRS loop in the horizontal plane is always clockwise and the posterior deviation of T in this plane between +75 and +122 degrees.

The cardiothoracic ratio is still within normal limits.

Patients with severe stenosis (right ventricular systolic pressure above 100 mm. Hg) show increasingly severe effort incapacity. The systolic murmur has a late peak and overrides the aortic closure whenever the right ventricular systolic pressure exceeds the systemic pressure. The pulmonic closure is not heard but may be recorded (aortopulmonic interval between 0.06 and 0.14 second). An increased fourth heart sound is common. The electrocardiographic findings include "pulmonary" P waves and T wave inversion beyond lead V_1. The vectorcardiogram shows marked posterior deviation of the T loop in the horizontal plane (between +80 and +170 degrees). The cardiothoracic ratio is increased.

The different methods of examination are compared; the reliability of the phonocardiogram and the value of careful auscultation alone as a gauge of the right ventricular systolic pressure and in the bedside selection of the operable patients are stressed.

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Aortic Valve Insufficiency in Arterial Hypertension*

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IN 1920, Osler[1] first recognized an aortic diastolic murmur in arterial hypertension; he believed that it was due to aortic insufficiency. Since that time it was noted that this murmur, which is extremely low in intensity and "high" in pitch, was very difficult or impossible to record by conventional sound tracings. This difficulty has been largely due to the fact that the usual amplifying and filtering technics fail to record murmurs which are low in intensity and which occur in that frequency area above 150 c.p.s.

The early attempts to record a faint high-pitched basal diastolic murmur in patients with rheumatic aortic regurgitation were made without success by McKee[2] and Arenberg[3] using a commercial phonocardiograph. On the other hand, Wells, Rappaport and Sprague[4] reported that they were able to record this murmur in some, but not all, cases of this type by using a Sanborn Tribeam phonocardiograph with stethoscopic and logarithmic microphones and interchangeable chest pieces. Butterworth, Chassin and McGrath[5] determined the frequency of the diastolic murmurs of aortic insufficiency with a series of electrical filters fitted to the auscultatory apparatus; they reported that most murmurs of aortic insufficiency had a frequency response of 100 to 200 c.p.s. Luisada's findings[6] with selective phonocardiography generally supported those of Butterworth et al.; he used a band-pass filter and noted that most aortic diastolic murmurs were recorded best when a frequency band of 150 to 200 c.p.s. was selected.

None of these reports, however, described the basal diastolic murmur heard in patients with hypertension. In our investigation, we were most interested in recording this diastolic murmur. We believe we have developed an improved phonocardiographic method which permits adequate registration of these low amplitude diastolic vibrations. Clinically, this murmur is characterized by its low intensity, its "high pitch" and its evanescence. It occurs immediately after the second heart sound and is sometimes "masked" by the marked loudness of this sound. The murmur is usually short in duration and is localized in a small area of the chest. It is heard best during expiratory apnea with the patient in the sitting position.

MATERIAL AND METHODS

In a series of 445 patients with hypertension seen on the wards of a large general hospital, twenty-seven were found to have a faint diastolic murmur on auscultation at the base of the heart (incidence of 6 per cent). Fifteen of these twenty-seven patients were studied by routine phonocardiography; ten of the fifteen underwent additional sound studies. Twenty-eight hypertensive patients without auscultatory evidence of a basal diastolic murmur were also studied.

All fifteen patients with a basal diastolic murmur had left ventricular hypertrophy, as revealed by physical examination, electrocardiography and posteroanterior films of the chest. Ten had a moderate to marked degree of hypertrophy; the other five had minimal enlargement. Roentgenograms of the chest showed that the ascending aorta was grossly normal in size and shape in thirteen of the fifteen patients. The other two had minimal dilatation of the aorta (posteroanterior projection). The range of the diastolic blood pressure in this group of fifteen patients, when taken in the recumbent position, was 110 to 160 mm. Hg (mean, 131 mm. Hg). The systolic blood pressure ranged from 180 to 260 mm. Hg (mean, 216 mm. Hg). The mean pulse pressure was 85 mm. Hg; the lowest pulse pressure was 40 mm. Hg and the highest was 130 mm. Hg. None of these patients had the peripheral vascular manifesta-

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tions of aortic insufficiency. There were no arrhythmias present at the time of the sound tracings.

Fifteen patients had a routine phonocardiogram (Sanborn Twin-Beam). Ten of these fifteen patients underwent special studies in which the twin-beam phonocardiograph was connected to a band-pass filter* and an amplifying stethoscope.† This apparatus was arranged as follows: an electromagnetic microphone was placed over the chest of the patient and plugged into the amplifying stethoscope. A cable was connected from the output of the amplifying stethoscope to the input of the band-pass filter. The output cable of the filter was plugged into the microphone outlet (input) of the sound amplifier of the twin-beam phonocardiograph (channel A). Thus, sound vibrations were transformed into electrical impulses, amplified, filtered, amplified again and recorded on channel A of the twin-beam; an electrocardiogram was recorded on channel B. The low- and high-pass frequencies of the filter were set at the desired limits and the tracing was made; for example, the low and very high frequency vibrations of the stethogram were cut off by selecting a frequency band of 150 to 200 c.p.s. The amplitude of the sound vibrations was controlled by the "loudness" knob of the amplifying stethoscope. In this manner we were able to regulate the sensitivity of the amplifying system so that the intensity of faint murmurs, heard on auscultation, might be satisfactorily reproduced. An audiophone was used to monitor this procedure. These studies were performed in a soundproof room with the patient in the recumbent position during expiratory apnea.

Sound tracings were obtained with both the bell and the diaphragm chest piece at the second right parasternal area (aortic), the second left parasternal area (pulmonic), the third, fourth and fifth left parasternal areas, the mid-precordium and the apex. An apex cardiogram and carotid pulse tracing were obtained on almost all patients. The apex cardiogram was used to time the diastolic events of the heart and the carotid pulse was used to denote the time of occurrence of the second heart sound.

Results

By using this method of selective filtering and amplifying, the basal diastolic murmur was successfully recorded in nine of the ten patients. From a study of these phonocardiograms, we suggest that this murmur is due to aortic valve insufficiency for the following reasons: (1) it immediately follows an accentuated second heart sound; (2) it is decrescendo in configuration; and (3) its point of maximal intensity is presumably located over the aortic valve. The murmur was recorded best at the left sternal margin in the third intercostal space, but its intensity was low even here. These diastolic vibrations were often visualized over a wide frequency range, i.e., between 150 and 400 c.p.s., but they were most readily demonstrated when a frequency band of 150 to 200 c.p.s. was selected. We were not able to record this murmur distinctly on the routine phonocardiogram, nor were these vibrations present when a frequency band of 20 to 80 c.p.s. was selected. Figure 1 portrays the results with both routine and specially filtered stethograms. Protodiastolic vibrations were not recorded in the twenty-eight hypertensive patients without auscultatory evidence of a basal diastolic murmur. The murmur was short in duration, frequently evanescent, and more easily detected during expiratory apnea, particularly with the bell chest piece. The presence of the diastolic murmur did not seem to bear any consistent relationship to the level of the systolic or diastolic blood pressure at the time of phonocardiography. Also, diastolic vibrations were not seen with any more frequency in patients who had an abnormally high pulse pressure (above 80 mm. Hg).

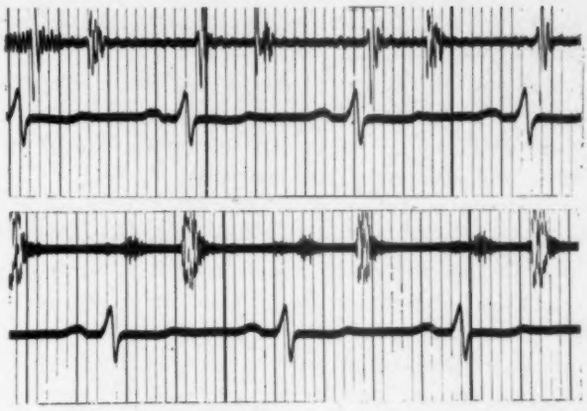

Fig. 1. Comparison of heart sounds and murmurs recorded from the third left parasternal area with a standard phonocardiograph (*upper tracing*) and a band-pass filter and further amplification (*lower tracing*). Distinct, early diastolic vibrations are not visualized in the upper, non-filtered stethogram. On the lower record, vibrations of medium to high frequency are seen following a high frequency second heart sound of increased amplitude and duration. To obtain this tracing, a band of 150 to 200 c.p.s. was selected.

The number of patients with the diastolic murmur is small. Therefore, it is difficult to make precise statements regarding the relationship of the age of the patient with the appearance of the murmur. The mean age was fifty-four

* Model 310AB, Krohnhite Instrument Company, Cambridge, Massachusetts.

† Model 256, Sanborn Company, Waltham, Massachusetts.

years. There were the same number of patients with the diastolic murmur above the mean age as below. Also, the entire hypertensive series was not age-distorted so that age does not appear to be an important factor in the development of the murmur.

A study of the graphic records of these fifteen patients revealed that the first heart sound was normal in amplitude and duration at both the apex and the aortic area. The mean duration of the second heart sound was 0.09 second at the aortic area, as compared to a mean duration of 0.07 second in the twenty-eight patients without aortic insufficiency. The amplitude of the second heart sound was increased in all patients and was usually greatest at the second right parasternal area. Five of the fifteen patients had a third heart sound of low frequency and amplitude and six patients had a low frequency fourth sound less than 0.07 second in duration. Three patients had low frequency vibrations in presystole greater than 0.07 second in duration, which we have called a presystolic murmur. This may represent the finding that Austin Flint has described in some patients with aortic insufficiency.

Systolic murmurs were noted frequently in our study. Vibrations were seen in early and middle systole in thirteen of the fifteen patients. They were usually of low amplitude and medium frequency, and were best visualized either at the apex or at the aortic area.

Summary

An improved phonocardiographic method for adequate recording of cardiac murmurs, characterized by medium-high frequency vibrations of low amplitude, is presented. This method utilizes a special band-pass filter and an amplifying stethoscope.

The faint, early, basal diastolic murmur which is present in some patients with arterial hypertension was satisfactorily recorded in nine of ten instances by this method, whereas the murmur was not recorded by the routine phonocardiogram. We believe that this murmur suggests insufficiency of the aortic valve.

On phonocardiography, the diastolic vibrations were low in amplitude and were more readily detected when a frequency band of 150 to 200 c.p.s. was selected. These vibrations immediately followed a second heart sound of increased amplitude and duration and were best visualized at the third left parasternal area. The presence of the murmur did not seem to be related to the level of the systolic, diastolic or pulse pressures at the time of the technical procedure.

Acknowledgment

We wish to thank Dr. Henry L. Taylor for his helpful suggestions in the preparation of this manuscript. We are also grateful to Mr. John Balogh for his technical assistance.

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Patent Ductus Arteriosus and High Altitude*

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IN A preliminary report published in 1953 it was suggested that patent ductus arteriosus and persistent interatrial communications were more likely to be found in patients born at high altitudes.[1] Since that time more patients with cardiovascular anomalies have been observed, and in the present article the influence of high altitude on the incidence of patent ductus arteriosus will be studied.

OBSERVATIONS

The first congenital anomalies of the heart diagnosed in 1944 in the Department of Cardiology of the Hospital Dos de Mayo were two patients with patent ductus arteriosus and one with atrial septal defect. It was noticed that all three had been born in the mining center of Cerro de Pasco or nearby at an altitude over 4,000 meters (13,200 feet). Since that time, to find out if this was a fortuitous occurrence, the exact place of birth was determined in each patient with a cardiac anomaly as well as the length of the stay thereafter. The possible influence of rubella was investigated when possible.

Twenty-seven thousand clinical histories from the Department of Cardiology as well as from private practice yielded 110 cases of patent ductus arteriosus. This diagnosis was confirmed in most cases by cardiac catheterization, operation or autopsy.

The Hospital Dos de Mayo is located in Lima, but the large migration to this city from the rest of the country provides a fairly representative sample of the population of Peru. Nevertheless it may be admitted that a predominant number of patients come from Lima, a large city of nearly a million inhabitants, located at an altitude of 156 meters (515 feet). In spite of this expected predominance of patients born in Lima, in order to be able to obtain statistical conclusions, the altitude of the place of birth of 1,000 consecutive patients admitted to the Department of Cardiology was determined. The same procedure was carried out with thirty-two patients with coarctation of the aorta.

RESULTS

Of the 1,000 admissions, the vast majority of patients were born at an altitude of under 3,500 meters (11,550 feet). Fifteen per cent of the general patient population of the hospital was born at an altitude of over 3,000 meters (9,900 feet), 9 per cent at an altitude above 3,500 meters (11,550 feet) and no more than 3 per cent at an altitude above 4,000 meters (13,200 feet) (Fig. 1).

The official census of Peru (1940) indicates that only 2.04 per cent of the total population of Peru lives at an altitude of over 4,000 meters. These data and those obtained from the hospital admission records correlate very closely.

Of the 110 patients with patent ductus arteriosus, nineteen (17.8 per cent) were born in areas where the altitude was between 3,000 and 3,500 meters, eleven (10 per cent) between 3,500 and 4,000 meters and twenty-two (20 per cent) in areas where the altitude was over 4,000 meters (Fig. 1).

According to the aforementioned data, 20 per cent of patients with patent ductus arteriosus came to the hospital from an altitude in which only 2.04 per cent of the total population of Peru lives, contributing only 3 per cent of general hospital admissions. In the statistical data obtained in 1953, 30.9 per cent of the patients with patent ductus arteriosus were born at an altitude of over 4,000 meters. This figure is probably more exact since only recently have children and infants been allowed to come to the Cardiac Department of the hospital. The great majority of these children are born in Lima. On the contrary, at the present time

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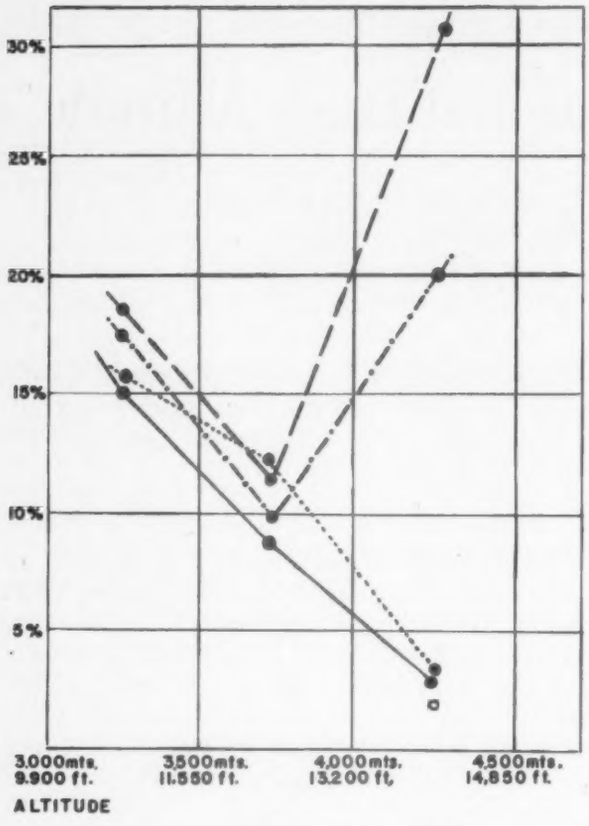

FIG. 1. Patent ductus arteriosus and altitude. ——— place of birth of 1,000 consecutive patients admitted to the hospital. — — place of birth of forty-two patients with patent ductus arteriosus (1953). —·— place of birth of 110 patients with patent ductus arteriosus (1959). - - - - - place of birth of thirty-two patients with coarctation of the aorta. O percentage of the population of Peru living at an altitude of over 4,000 meters (13,200 feet).

as before, patients with patent ductus arteriosus coming from high altitudes are young adults or persons over twenty years of age.

Confirming this impression is the fact that among the 110 patients with patent ductus arteriosus, thirty-one were born in Lima (altitude 156 meters) and eleven in Cerro de Pasco (4,400 meters). This means that nearly three times as many patients with patent ductus arteriosus were born in Lima than in Cerro de Pasco, but it should be noted that the population of the former is twenty-three times that of the latter.

In this series, rubella appears to be a factor in only three patients with patent ductus arteriosus. All were observed at sea level.

As could be expected, patency of the ductus arteriosus at high altitude was largely observed in "mestizos," but in Cerro de Pasco it was also observed in children whose parents were pure Spanish, American and Japanese.

From the foregoing data it seems certain that high altitude is a factor in determining persistence of the ductus arteriosus, its influence becoming evident at altitudes of over 4,000 meters. As may be seen in Figure 1, altitude does not seem to be an etiologic factor in coarctation of the aorta.

COMMENTS

After the first report concerning the influence of altitude on the frequency of certain cardiovascular anomalies, other observations have been made. Marticorena[2] examined 3,000 school children at high altitudes of between 3,730 and 4,843 meters, and found nine cases (0.3 per cent) of patent ductus arteriosus. Rossina[3] examined 8,000 school children in Lima (altitude 156 meters) and found only four cases (0.05 per cent) of patent ductus arteriosus. According to these data, persistence of the ductus arteriosus is six times more frequent in people born at a high altitude than in those born at sea level. Rodríguez-Larraín[4] arrived at the same conclusion after examining applicants to the police force.

The influence of high altitude in determining several anomalies has been proved experimentally by Ingalls.[5] The closing of the ductus arteriosus is probably due to various causes, not all of which are understood. It is interesting to note that Senac,[6] in 1749, believed that the ductus arteriosus remained patent when the respiratory function was impeded. It is presumed that after birth a "functional" obliteration takes place because of an equilibration of the pressure of the pulmonary artery and aorta.[7] In 1953, it was presumed that a mechanical factor in the pulmonary circulation as well as the low oxygen tension were responsible for the persistence of the ductus arteriosus at high altitude. Rotta et al.,[8] studying the pulmonary circulation in normal persons at sea level and at high altitudes, found somewhat higher pulmonary pressures at high altitude. We do not know the effect of altitude on the pulmonary circulation after birth. On the other hand, there is experimental evidence[9,10] that oxygen is a very important stimulus for the closing of the ductus arteriosus.

SUMMARY

Patent ductus arteriosus is more likely to be found in patients born at high altitudes. The effect becomes manifest at altitudes of over 3,000

meters and is most evident at altitudes of over 4,000 meters.

It is presumed that mechanical factors affecting the pulmonary circulation as well as the lower oxygen tension may influence persistent patency of the ductus arteriosus.

High altitude does not appear to be an etiologic factor in coarctation of the aorta.

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The Double Femoral Sound*

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IN CERTAIN cases of acquired or congenital heart disease a double femoral sound can be heard in the groin. Several patients presenting this finding will be described and discussed.

CASE REPORTS

CASE 1. A. M., a thirty-six year old man, entered the hospital with dyspnea and progressive edema. Examination showed marked edema, an enlarged liver and ascites; the pulse rate was 90 per minute, the blood pressure was 125/45 mm. Hg. A loud machinery murmur was heard in the precordium, more intense in the third left intercostal space; a presystolic gallop was heard at the precordium. Pulsations were observed in the jugular veins and in the veins of the upper extremities. In the groin a double sound was heard; the loudness of these sounds depended on the degree of pressure exerted by the bell of the stethoscope.

Fluoroscopic examination showed an enlarged and hyperactive heart; pulsations of the aorta were marked. The *electrocardiogram* suggested right ventricular hypertrophy and the prominent P waves were compatible with auricular enlargement.

The *phonocardiogram* taken from the groin showed double femoral sounds; in the same region double pulsation was recorded (Figs. 1 and 2). In the *femoral venous tracing*, a double wave was present (Fig. 2). The brachial arterial pressure tracings were similar to those recorded in patients with aortic insufficiency and the pressure tracings of the cephalic vein showed a giant presystolic wave (Fig. 3). In the jugular pulse and in the right auricle, prominent A waves were seen.

Cardiac catheterization disclosed elevated pressures in the right auricle and right ventricle (right auricle, 35/15 mm. Hg; right ventricle, 100/20–35 mm. Hg). It was not possible to pass the catheter into the pulmonary artery.

The clinical diagnosis was aneurysm of the sinus of Valsalva rupturing into the right ventricular cavity. *At autopsy*, an aneurysm of the sinus of Valsalva was found but it did not open into the right side of the heart. The sac bulged into the outflow tract of the right ventricle, producing a subpulmonic stenosis.

CASE 2. M. A., a twenty-nine year old man, was admitted to the hospital with severe heart failure. Examination disclosed blood pressure of 140/90 mm. Hg and pulse rate of 110 per minute. An apical

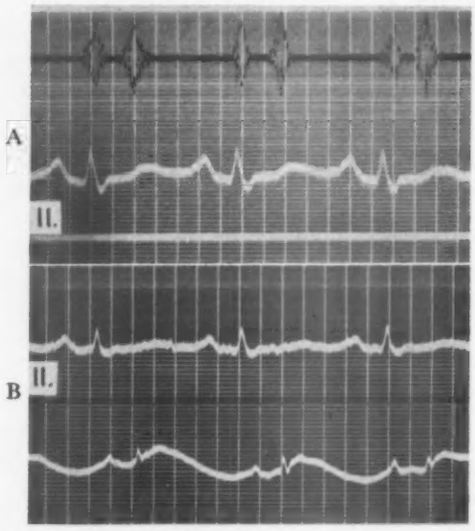

FIG. 1. Case 1. A, phonocardiograms from groin showing presystolic and systolic femoral sounds. B, double femoral pulsations from same area.

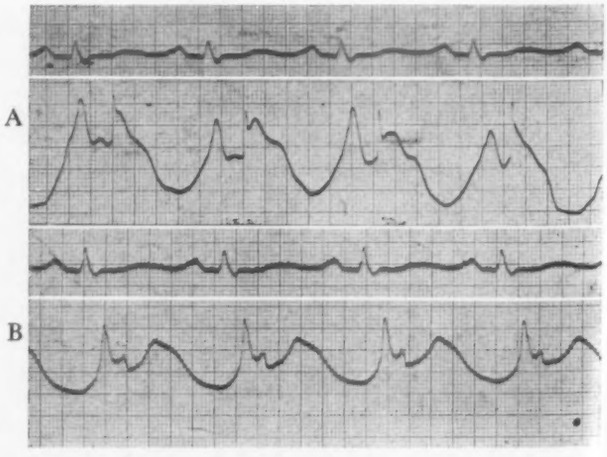

Fig. 2. Case 1. A, presystolic and systolic double femoral pulsations. B, femoral venous pressure tracing showing double pulsation.

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systolic murmur (grade 3) and a diastolic aortic murmur (grade 3) were present. Along the upper left sternal region an intense systolic-diastolic murmur was heard. In the femoral region, when the pressure of the stethoscope was slight, a double sound was present; when pressure was increased a double murmur of Duroziez was heard.

Fluoroscopic examination showed an enlarged heart with hyperactive aorta. In the *electrocardiogram* the P waves were prominent. Otherwise the tracing was within the normal range. Soon after, fever appeared. Later, auricular fibrillation developed and the double femoral sound disappeared. Heart failure could not be controlled and the patient died.

The clinical diagnosis was congenital heart disease and subacute bacterial endocarditis. *At autopsy*, verrucous endocarditis of the aortic valves and a high interventricular septal defect were found.

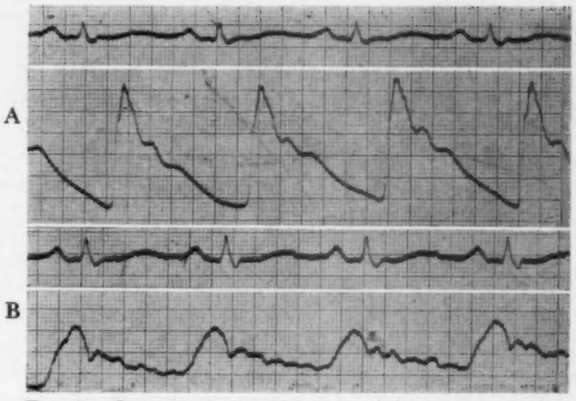

FIG. 3. Case 1. A, brachial arterial pressure tracing showing high pulse pressure. B, cephalic venous tracing showing prominent presystolic wave.

CASE 3. D. G. L., a thirty year old woman, had a history of heart failure four years before the present admission. On three occasions she had had syncope following physical effort. She also had experienced repeated attacks of paroxysmal auricular tachycardia. When seen in the outpatient clinic, the pulse rate was 90 per minute and frequent ventricular extrasystoles were present; the blood pressure was 130/80 mm. Hg. The pulmonic second sound was accentuated; a soft diastolic pulmonary murmur was heard along the sternal border. The jugular veins were congested and pulsating. A double femoral sound was evident.

The *teleoroentgenogram* showed right ventricular hypertrophy and prominent hilar pulmonary vessels; the fields of the lungs were clear. The *electrocardiogram* suggested auricular enlargement and right ventricular hypertrophy. Three weeks later the P-R interval in the electrocardiogram was changing and frequent ventricular extrasystoles were present.

Simultaneous electrocardiograms and *phonocardiograms* from the femoral region were recorded (Fig. 4). The interval between the two femoral sounds changed according to variations in the P-R interval. When the

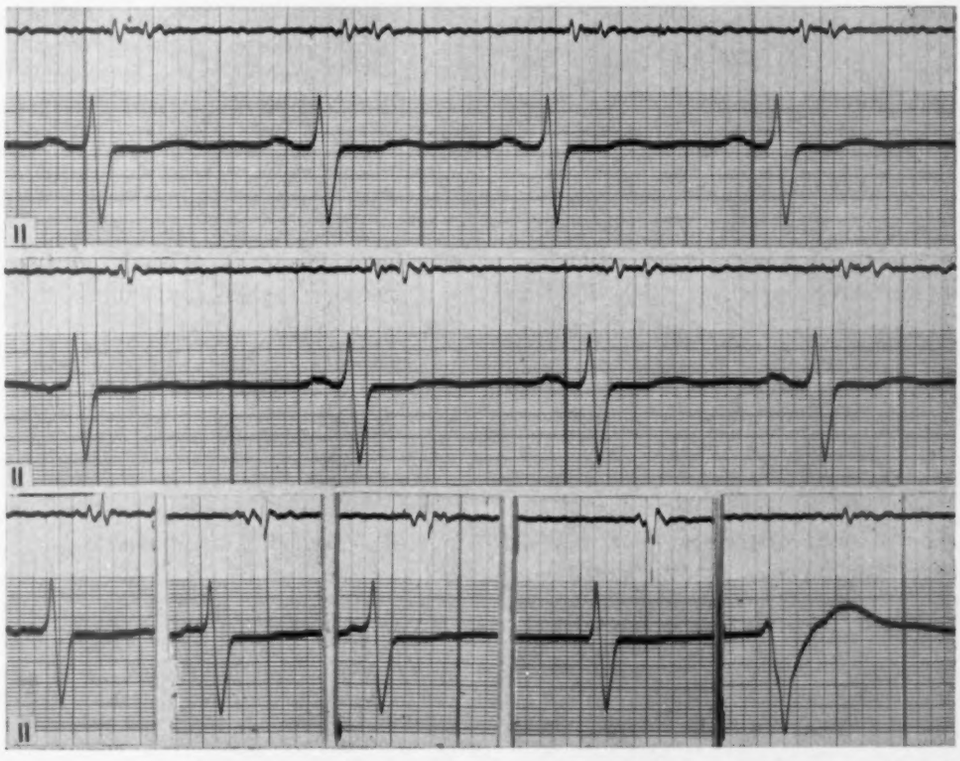

FIG. 4. Case 3. Simultaneous phonocardiograms and electrocardiograms from the femoral region. The interval between the two femoral sounds varies according to the changing P-R interval. A single sound is present during a ventricular premature beat.

auricular and ventricular activation were simultaneous, only one loud femoral sound was recorded. During ventricular premature beats a single faint sound was present. It was then evident that the first femoral sound was of atrial origin.

The clinical diagnosis was essential (idiopathic) pulmonary hypertension. The patient died in intractable heart failure.

CASE 4. P. N. A., a fifty-four year old man, entered the hospital with heart failure, orthopnea, fever and yellow sputum. The pulse rate was 120 per minute and blood pressure was 110/80 mm. Hg. The second pulmonic sound was accentuated and a presystolic gallop was heard. The jugular veins were congested and pulsating. The liver was enlarged and there was marked edema of the lower extremities. A double femoral sound was heard. Rales were audible in both lungs.

Roentgenographic examination of the chest showed hilar congestion with relatively clear lung fields. The heart was moderately enlarged. The *electrocardiogram* suggested acute cor pulmonale.

The clinical diagnosis was acute or subacute cor pulmonale of uncertain cause. *At autopsy*, the right auricle and ventricle were moderately dilated; otherwise the heart was normal. In both lungs small condensed regions were observed scattered in the parenchyma. The histologic examination demonstrated "multiple thromboses of the small arterioles in both lungs."

CASES 5, 6, 7 and 8. The double femoral sound was heard in four other patients with diagnoses of patent ductus arteriosus with pulmonary hypertension, pure pulmonic stenosis, chronic cor pulmonale with hypoxia, and acute cor pulmonale, respectively.

COMMENTS

Unusually large waves in the jugular venous pulse (giant A waves) due to hyperactivity of the right auricle have often been described in patients with acquired and congenital heart disease.[1,2]

In 1943, Sensenbach and Hutaff[3] described systolic pulsations of the veins in the extremities in a patient with auricular fibrillation and complete heart block. In 1941, Hallock and Clarke[4] observed generalized systolic pulsations of the veins in a patient with rheumatic heart disease and auricular fibrillation. In patients with aneurysm of the sinus of Valsalva, unusual venous pulsations have been observed in the jugular and sublingual veins[5] and "pistol shot" sounds have been heard in the groin.[6]

In 1956, Dock[7] described a presystolic sound in the jugular veins in patients with right ventricular diastolic hypertension. Dagnini,[8] in 1894, observed visible and palpable presystolic waves that he thought were of atrial origin in the groin of a patient with tricuspid stenosis. In 1941, Pezzi and Gasperini[9] observed similar presystolic waves in three patients with congenital heart disease, two of whom had pulmonic stenosis. Aitchison, Duthie and Young,[10] described pulsations at the same rate as the atrium easily palpable in both groins in a patient with transposition of both arterial trunks and complete atrioventricular block.

To our knowledge, the double femoral pulsation has never been described as an audible sound. The auricular origin of the first femoral sound seems to be certain. The second femoral sound is related to ventricular contraction. In one patient (Case 2), the double femoral sound disappeared when auricular fibrillation ensued. In another (Case 3), the presence or absence of the sounds, their intensity and the interval between the two sounds depended upon variations of the P-R interval and the occurrence of ventricular extrasystoles.

The auricular sound heard in the groin is produced by a powerful contraction of the right atrium. This occurs when the resistance to right ventricular filling has increased or when right ventricular diastolic pressure is high. For the foregoing reasons the auricular sound has been heard in several conditions: left-to-right shunts (Case 2), pulmonary hypertension (Cases 3, 5 and 7), pulmonary embolism (Cases 4 and 8), pulmonary stenosis (Case 6), and in a patient in whom the circulation was blocked within the right ventricle, simulating subpulmonic stenosis (Case 1). We suspect that the auricular sound may be present in certain cases of tricuspid stenosis. The auricular sound has not been recorded in tricuspid insufficiency probably because, very often in this condition, the auricle empties into a large ventricular cavity. Forcible contractions of the right atrium are only possible when the auricular muscle has not been seriously damaged. We may suspect that in a number of cases the auricular sound disappears when, after a period of time, the auricular muscle fails.

SUMMARY

A double femoral sound is described in patients with congestive heart failure of varied etiology. The factor common to all patients was a powerful atrial contraction secondary to increased right ventricular diastolic pressure or increased resistance to right ventricular filling. The first sound is produced by atrial systole

transmitted by the venae cavae to the femoral veins; the second sound by left ventricular systole transmitted by the aorta to the femoral arteries.

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The Neuropsychiatric and Psychologic Significance of Cerebrovascular Damage (Strokes) Following Rheumatic Heart Surgery*

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An opportunity to observe the impact of cerebral vascular complications was presented in connection with a long-term study of seventy-five cardiac patients, forty-eight of whom underwent heart surgery.[1,2] This study included periodic pre- and postoperative medical, psychiatric, neurologic and psychologic examinations, with up to four years follow-up. A preoperative history of cerebral vascular accidents was elicited in five (8.9 per cent) of the fifty-six patients with rheumatic heart disease. Thirty-three underwent mitral commissurotomy. In the immediate postoperative period three patients (9.1 per cent) suffered cerebral insults. Other studies (Williams,[3] 8.5 per cent; Bailey,[4] 5.1 per cent; and Ellis,[5] 7.3 per cent) show a comparable incidence of diagnosed cerebral vascular complications associated with mitral valve surgery.

Thus, in our study, the incidence of known cerebral vascular complications rises to 18 per cent in the patients with rheumatic heart disease undergoing mitral surgery. Since almost one in five such patients may suffer cerebral involvement, in either the pre- or immediate postoperative period, it is important to determine the significance of such damage. The psychiatric and neurologic data of the three patients who suffered such problems in the immediate postoperative period will be presented in some detail. The psychologic test data will be discussed subsequently.

CASE REPORTS

CASE 1. A single, steadily employed factory laborer underwent a mitral commissurotomy at the age of thirty-nine. The patient was the youngest of seven siblings, born of devout Catholic parents in the industrial section of a large midwestern city. The father was a domineering, outgoing, steadily employed lithographer. The mother, who was more permissive and less stern, died of an unknown heart disease when the patient was fourteen. One of the patient's older sisters filled the maternal role and continued to do so up to and after the time of operation. In his social adjustment within and outside the family, the patient seemed to remain in the role of the "youngest." Neither mature heterosexual adjustment nor advancement to position of authority and responsibility was evident in his social history. Although the cardiac condition became definitely known at the age of twenty-three, persistent symptoms of fatigue and palpitation did not occur until two years prior to surgery, when the patient was thirty-seven.

A preoperative neurologic examination revealed generalized hyperactivity of the deep tendon reflexes and minimal right facial assymmetry. During the operation the surgeon reported that he felt particles of calcium crumbling from the valve edge.

Thirty hours after surgery there was a sudden onset of lethargy attended by dilatation of the right pupil

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This research project was originally supported by the Schermerhorn Fund. Continuation of follow-up studies has been made possible by a research grant, No. H 4915, from the U. S. Public Health Service, and by a grant from the Chicago Heart Association.

TABLE 1
Patients with Cerebrovascular Complications Following Mitral Commissurotomy

Historical data	Case 1	Case 2	Case 3
Age at surgery	39 years	39 years	46 years
Occupation	Factory laborer	Nurse reception	Housewife
Educational level	11th grade and trade school	High school and nurses training	High school
Impairment of normal childhood activities	None	None	None
History of rheumatic fever	Bedridden only several weeks in childhood	Chorea at age 10	Fever and joint pains at ages 6 to 8
Duration of marked limitation of activity prior to surgery	5 years	Episode of several weeks at age 20	3 years
Major neurotic or psychotic decompensation	None	None	None

and the presence of a Babinski sign on the right and partial expressive aphasia. This was followed within twenty-four hours by loss of abdominal reflexes and the appearance of bilateral Babinski signs. Mental cloudiness gradually diminished until the patient's discharge twenty-five days later.

Findings two years after surgery revealed residual weakness of the left arm on finger-to-nose and Rossolimo sign on the right.

CASE 2. A nurse-receptionist underwent a commissurotomy at the age of thirty-nine about one week after a sudden admission to the hospital because of pain in the lower right side of the abdomen and right leg, which was diagnosed as systemic arterial embolization. The patient was the oldest of five siblings, all but the youngest of whom were girls. The patient's father, a bank clerk, was described as "hard-headed and rarely affectionate." Her mother died of hypertensive heart disease when the patient was fourteen years old. She adjusted with difficulty to the stepmother whom the father married two years after his wife's death. Although a short episode of chorea occurred when the patient was ten, limitation of normal activities was not imposed during childhood. The patient first learned of her cardiac disease at the age of twenty-one. During nurse's training she had difficulty with authoritarian nursing instructors. After graduation she became a nurse-receptionist in a physician's office. Divorce from her husband after four years of marriage, when she was twenty-eight, was attributed to difficulty with a domineering mother-in-law. The patient also got along poorly with her sisters who resided in the same city.

At commissurotomy, a large thrombosis was found in the left auricle. Four hours following operation, mild right hemiparesis attended by mental dullness and lethargy became evident. Weakness of the extremities on the right, with flattening of the right side of the face, occurred and became more severe. Eighteen hours after operation, the patient was noted to become aphasic gradually. Twenty-four hours postoperatively, absence of the pulsation of the left internal carotid artery was discovered. Deep tendon reflexes, however, remained symmetrical and no pathologic toe or hand signs were elicited. Abdominal reflexes were absent. The patient's condition gradually improved, the severe aphasia diminished and there was return of strength in the right arm during the ensuing weeks. She was discharged three weeks after surgery.

A neurologic examination two years later revealed a mild expressive aphasia, minimal evidence of right facial weakness, and slight weakness and minimal hypesthesia of the right arm.

CASE 3. A widow, mother of six, underwent a commissurotomy at the age of forty-six. She was born in a small midwestern town, the second eldest in a sibship of seven. Both parents were of German extraction and devout Catholics. The father was described as firm and strict, the mother as permissive and easily manipulated by the children.

In childhood significant limitations of activities were not imposed by the rheumatic fever. The patient was graduated from high school and worked as a clerk until her marriage at the age of nineteen. The husband, who was employed as a milkman, was a poor provider, and died leaving the patient, then aged thirty-six, pregnant, with five children, ranging in age from six months to fifteen years, and few financial resources. The patient worked as a waitress until the age of forty-three, when she was incapacitated by her dwindling cardiac reserve.

Prior to surgery the patient presented no abnormal neurologic findings. Twelve days after an uneventful commissurotomy, the patient, while using the bedpan, suddenly complained of a left temporal headache. A neurologic examination shortly thereafter revealed dilatation of both pupils and weakness of the right arm and leg which, within hours, progressed to almost total paralysis, but the deep tendon reflexes remained symmetrical. Seven hours later, only a

TABLE II
Neurologic Complications

Data	Case 1	Case 2	Case 3
Preoperative neurologic status	Generalized hyperreflexia; left face pulled away slightly better than right	Essentially normal	Essentially normal
Possible embolic source at surgery	Calcium particles from valve edge	None apparent	Auricular thrombus 2 by 2 by 1 cm. removed
Onset after surgery	30 hours	4 hours	12 days
Major findings	Lethargy; transient expressive aphasia; loss of abdominal reflexes; bilateral Babinski signs	Hemiparesis, right; lethargy; aphasia, severe; absent abdominal reflexes	Dilated pupils bilaterally; weakness of right arm and leg; hypesthesia of right leg; minimal amnesia
Residuals	Rossolimo, right; arm weakness, left	Expressive aphasia; hemiparesis, right, minimal	Hypesthesia lower right leg; alternating movements slightly impaired on right
Impression	Cerebral infarctions, small bilateral, embolic	Left cerebral infarction; left common carotid occlusion	Left cerebral infarction, small, embolic

mild paresis of the right arm and leg persisted, accompanied by some hypesthesia in the lower right leg. The patient was partially amnesic for the period of the disturbance. Strength gradually improved until her discharge one month later.

A neurologic examination two years after discharge revealed only minimal hypesthesia in the lower third of the right leg and slight impairment of rapid alternating movements on the right.

NEUROPSYCHIATRIC AND PSYCHOLOGIC DATA

The relevant background data of these patients are summarized in Table I. The preoperative and neurologic findings after the cerebrovascular accident are given in Table II.

The psychologic test battery administered to our patients was extensive and included eight subscales of the Wechsler-Bellevue Intelligence Scale,[6] a block-sorting type concept formation test,[7] tests for cortical involvement,[8] the Gottschaldt Concealed Figures,[9] the Street-Gestalt Completion test,[9] the Draw-A-Person test and other projective technics.

Thus our study provided the unusual opportunity to obtain a complete psychological test battery on each of the three patients with cerebrovascular accidents occurring after commissurotomy before the insult to the central nervous system occurred. We are, therefore, in the fortunate position of being able to compare each individual's production before the injury to the brain with his production during the period immediately after the injury, as well as long-term follow ups. We shall now consider some of the changes on a number of tests.

Handwriting: The two patients (the laborer and the nurse) in whom expressive aphasia developed following commissurotomy, showed marked changes in their ability to write stories about their projective drawings. Figure 1 depicts samples of handwriting obtained from these two patients at the time they were tested before and after surgery. These samples are part of the produced stories which they were asked to write about the person they drew at the respective testing session.

Changes were evident not only in a deterioration of content, but also in an impairment in the motor aspects of story writing ability of the two patients with aphasia. When comparing the pre- and postoperative data, there are apparent striking changes in pencil pressure, a general decrease in steadiness of writing and legibility; particularly, some words are scribbled over and retraced with considerable pencil pressure, but without resultant clarity—in a sense, paralleling the expressive aphasia observed in the speech patterns of these two patients.

The marked changes in writing of meaningful material may be of particular interest, for usually samples of patients' handwriting before injury to the brain are easily available in the form of letters or notes, and comparisons with writing samples after injury can readily be made with some diagnostic implications. Such comparisons can be of importance in pinpointing the time of the occurrence of cerebral damage when it is not brought to the attention of a physician for some time, or if it is important to determine if previous episodes occurred.

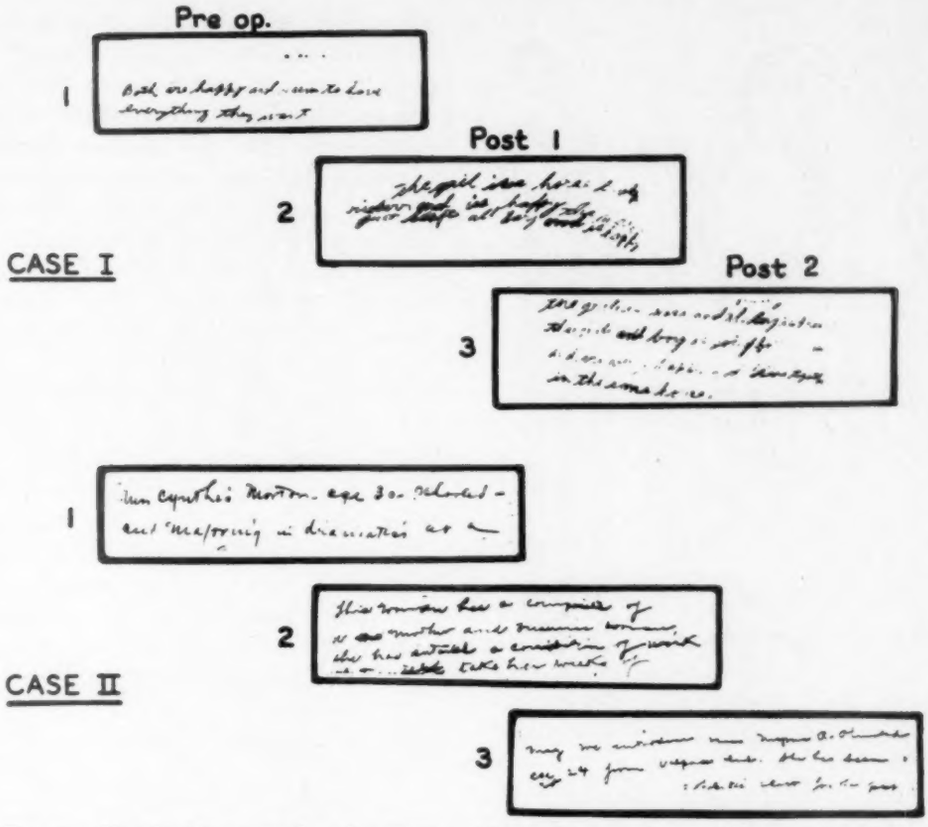

FIG. 1. Handwriting samples of patients with cerebrovascular accidents and aphasia following commissurotomy before and after injury.

It is evident in the second retest after surgery that there is considerable recovery of writing ability one year after injury in both patients in whom expressive aphasia developed. The third patient (the housewife) in whom signs of aphasia did not develop, did not show any noticeable changes in writing.

Draw-a-Person Test: As a rule, an individual's drawings of human beings are remarkably consistent from test to retest. It is therefore noteworthy when marked changes in this ability occur when an individual is retested after only a few weeks. The drawings of a man by the three patients are reproduced in Figure 2.

In Figure 2 the drawing of a man by each of the three patients before commissurotomy is compared with the same patient's drawing at the first retest after injury, and a year later.

There is evident clumsiness, considerable change in the size of the drawing, and general deterioration in the ability to produce an integrated picture of a person in the retest immediately after injury, as compared with the preoperative test. In view of such gross changes, a discussion of the various detailed signs shall be omitted. The change is particularly striking in Case 1 (the laborer).

Unfortunately, in Case 2 (the nurse) the technical reproduction is somewhat faulty because some parts of the outlines of the drawing were so much fainter that they could not be reproduced photographically. On the original drawings it can be clearly seen that in the period before injury the patient produced a skillful drawing of a sophisticated-looking man holding a cigarette. She handled the pencil strokes with precision and determination. After the cerebral insult her ability deteriorated and she produced a constricted drawing of a small, hunched man. There was appreciable decline in motor control, which was particularly noticeable in her inability to control the pencil strokes when attempting to round off the end of the left shoulder, in the outlining of the left arm and hand, and the belt. This first drawing after injury was obtained two months after mitral commissurotomy and diagnosed cerebral ischemia, as the patient was not able to make any drawings for several weeks.

In Case 3 (the housewife) the first drawing

FIG. 2. Drawings of a man by patients with cerebrovascular accidents following commissurotomy. A, preoperative. B, first test after injury. C, one year later. *Top*, Case 1. *Middle*, Case 2. *Bottom*, Case 3.

after injury was obtained six months after mitral commissurotomy for this patient refused to draw a person at the retest immediately after surgery, that is, three weeks after surgery. Even half a year after the cerebrovascular accident, however, this patient's drawing still showed a marked impairment, with clumsiness and unsteadiness of outlines and constriction in size, representing a much smaller, helpless and childlike man. There was transparency of sleeves and pants, lack of eye pupil and ear and other signs of partial loss of ability, as compared with the patient's preoperative drawing.

In each of the three cases, improvement in the ability to draw a person was apparent at the second retest after surgery, i.e., one year after injury.

The drawings as well as the handwriting samples of these patients were compared with the productions of twenty-six other patients who underwent and survived mitral commissurotomy and were similarly tested pre- and postoperatively. It was determined that these changes were not characteristic of such patients in general.

Intellectual Test Performances: While there are many published studies concerned with the evaluation of intellectual deficits in persons with injury to the brain, because of inaccessibility of data they are based, with few exceptions, on comparisons with non-injured subjects, rather than on direct observations of the intellectual test performance before and after injury of patients with involvement of the central nervous system. Relevant test data concerning relatively young adults who suffer strokes are particularly scarce.

Figure 3 represents the group mean performance of the three patients with injury to the brain on the eight subscales and the verbal, prorated performance, and full-scale I.Q.'s on the Wechsler-Bellevue Intelligence Scale for Adults (Form I). The heavy black line represents the preoperative averages on the various subscales. Only ability on Digit Span and Arithmetic is appreciably low. This we found to be characteristic of groups of cardiac patients in general, i.e., those with rheumatic as well as congenital cardiac disorders. The first retest after surgery, indicated by the dotted outline, represents the changes in intellectual functioning upon retest with the same intelligence scale.

It is readily apparent that, except for the Arithmetic subscale, which was already low

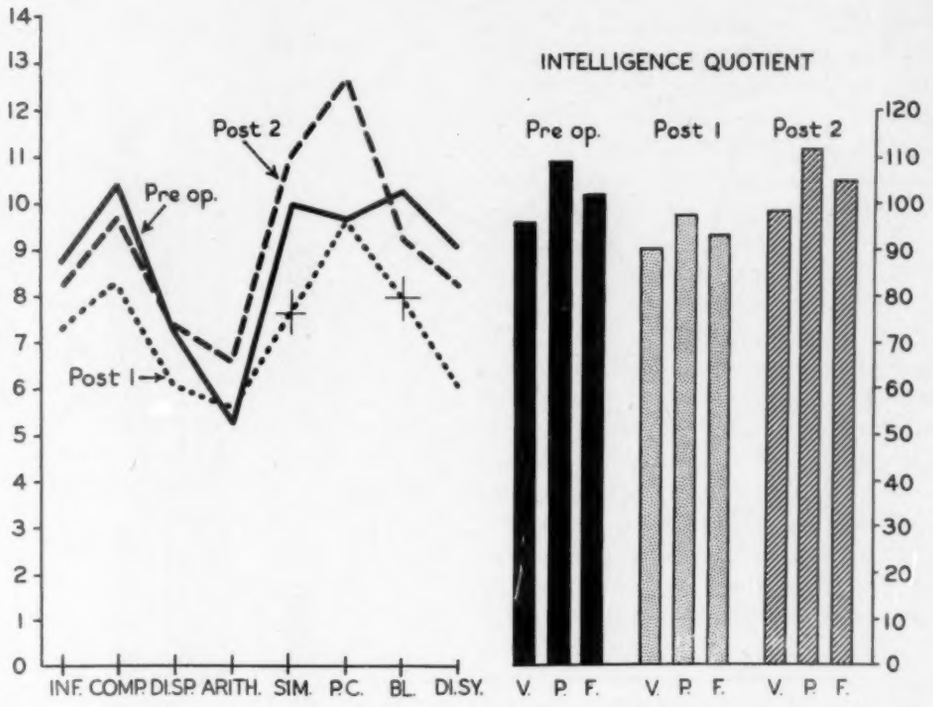

FIG. 3. Wechsler-Bellevue group mean scores, before and after injury, of patients with cerebrovascular accidents following commissurotomy. V = verbal IQ; P = performance IQ; F = full scale IQ.

preoperatively, and Picture Completion, which remain at the same level, all the other subscales show a decrease in performance ability. Average losses in Block Design, Digit Symbols, Comprehension and Similarities exceed two weighted points per subscale. The broken outline, representing the retest one year later, however, tends to approximate closely the preoperative profile on several subscales, and even exceeds it in Arithmetic, Similarities and Picture Completion weighted mean scores. This appears to demonstrate a noteworthy amount of recovery of intellectual functions.

The average verbal, performance and full-scale I.Q. are depicted on the right side of Figure 3. The heavy black bars (preop.), representing the preoperative I.Q. averages, are in the normal average range, and are clearly higher than the first postoperative I.Q.'s, represented by the dotted bars (postop. 1). The retest immediately after injury shows an approximate mean loss of about 8 I.Q. points in verbal abilities and 12 I.Q. points in performance I.Q., as compared with the preoperative mean I.Q. scores. The full-scale I.Q., a composite of these two, indicates that the average after injury is 10 I.Q. points lower.

One year after injury to the brain (postop. 2), the verbal, performance and full-scale I.Q. each exceeds the respective preoperative group mean I.Q. This indicates a fair degree of recovery. Some of the gain reflected in increase of subscale and I.Q. scores is due to practice effect, i.e., a consequence of repeated testing with the same instrument. A comparison with a group of twenty-six other patients who underwent mitral commissurotomy and were similarly tested, indicates that the increases in the score one year later in patients with cerebrovascular accidents after commissurotomy are only slightly lower than expected in repeated testing.

Figure 4 represents the Wechsler-Bellevue Intelligence Scale group mean profile of five patients with mitral stenosis who suffered cerebrovascular accidents two to nineteen years prior to evaluation for cardiac surgery. The profile indicates that, except for a low score in Digit Span and a tendency for a lowered score in Arithmetic (a general characteristic of cardiacs), no marked impairments are evident. The subscales which were most strikingly impaired in the retest immediately after injury in the patients who had cerebrovascular accidents after commissurotomy do not show appreciable deviations from other non-impaired subtest mean weighted scores in the group of rheumatic cardiac patients tested two to nine-

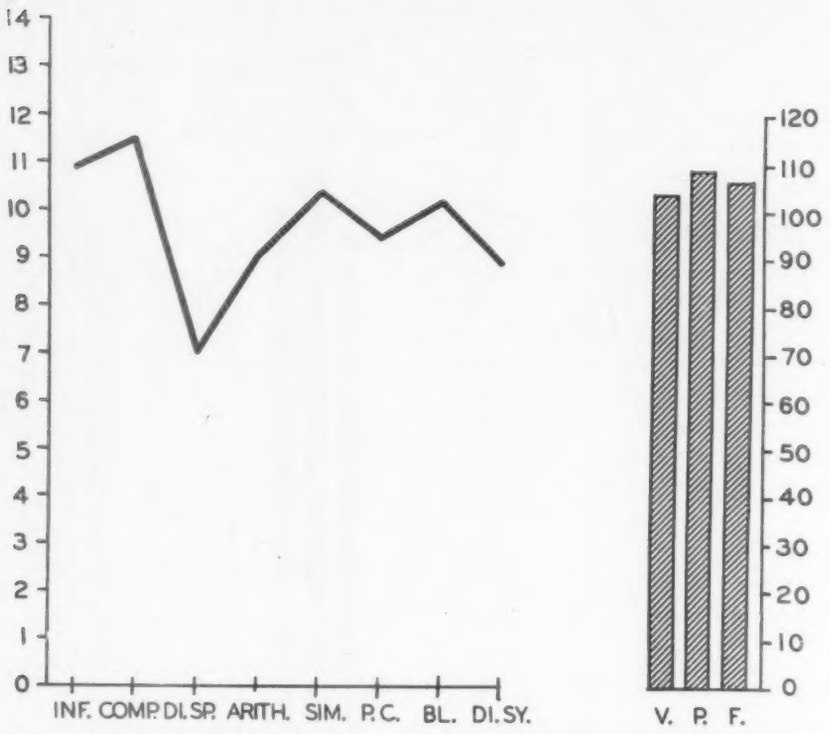

FIG. 4. Wechsler-Bellevue group mean scores of patients with mitral stenosis and history of cerebrovascular accidents two to nineteen years following stroke.

teen years after occurrence of cerebrovascular accidents.

Organicity Tests: Figure 5 represents six tests assumed to be sensitive to cerebral damage. The three tests in the upper row, Block Design, Digit Symbols and Digits Backwards, are parts of the Wechsler-Bellevue Intelligence Scale. The other three tests, in the lower row, were especially included in this discussion because they have been found by various investigators to be diagnostic tests for damage to the brain. The Concept Formation Test for Generalized Deterioration and the Visual Illusions are parts of the Yacorzynski-Northwestern Battery for Organic Involvements. The Gottschaldt Figures have been independently demonstrated to be sensitive to cerebral damage.[10,11]

The average performance ability of the three patients with cerebral complications after commissurotomy decreases in the immediate postoperative period on each of the six tests, as is evident in a comparison of the solid black bar, representing the preoperative level, with the respective dotted bar, representing the immediate postoperative performance on each organicity test.

The respective diagonally striped bar, representing one year postoperative performance, and white bar, representing two- to four-year postoperative performance, show various degrees of improvement in the individual tests. With the exception of Digits Backwards and Digit Symbols, the two- to four-year postoperative group mean scores reach or exceed the preoperative level. Consequently, it appears that recovery processes are present in most functions represented.

As the respective tests are subject to various amounts of practice effect, it is important to keep in mind that the actual score decrease following cerebrovascular accidents on all tests discussed in this paper is somewhat more pronounced than is apparent, and the recovery less complete than the scores indicate.

In conclusion, the psychologic examinations of patients with diagnosed cerebrovascular damage following mitral commissurotomy indicated an initial widespread impairment of psychologic functioning following the cerebrovascular accident, and gradual recovery of diminished abilities almost to the preoperative functioning level, with minor residuals remaining in perceptual motor abilities and personality functioning after three years.

Intelligence, as measured by the Wechsler-Bellevue Scale, indicated almost complete

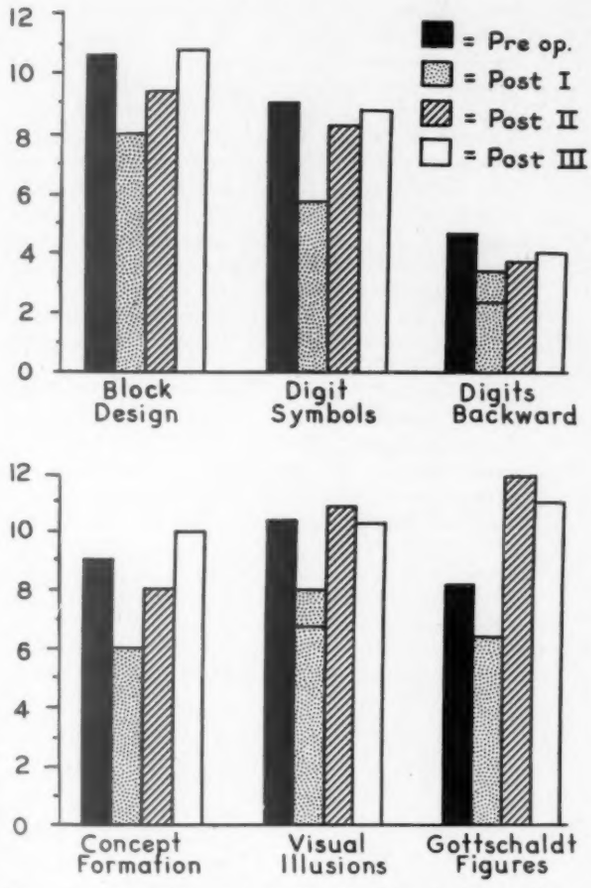

FIG. 5. Organic test battery of patients with cerebrovascular accidents following commissurotomy.

return to the preoperative level within a few years.

Psychiatrically, two of the three patients with postoperative neurologic deficit made satisfactory readjustments and returned to previous occupations, while the third, a nurse with residual aphasia, had definite rehabilitation difficulties, and could not return to her full-time professional job.

No improvement in cardiac dynamics, as measured by recatheterization studies and exercise tests during the second postoperative year, was observed in any of these three cases.

Among many factors influencing readjustment in cerebrovascular accident cases after commissurotomy, outstanding was availability of supportive individuals in the patient's milieu, and his ability to utilize them in his day-to-day rehabilitative efforts.

SUMMARY

A study of seventy-five cardiac patients, including periodic medical, psychiatric, neurologic and psychologic examinations, was made, with a four-year follow up. A preoperative history of cerebral vascular accidents was elicited in five (8.9 per cent) of the fifty-six patients with rheumatic heart disease. Thirty-three of these patients underwent mitral commissurotomy. In the period immediately after commissurotomy, cerebral vascular complications (strokes) developed in three (9.1 per cent) patients. Thus, the incidence of known cerebrovascular complications rises to 18 per cent in the patients with rheumatic heart disease undergoing mitral surgery. Consequently, almost one in five such patients may suffer cerebral involvement, in either the pre- or immediate postoperative period.

Detailed examinations were made preoperatively, and repeated postoperatively at three weeks, six months and yearly, up to four years.

Psychologic tests included measures of intelligence, organic involvement of the brain and projective technics. Psychiatric history, mental status and neurologic examinations were also repeated periodically. Medical follow-ups included recatheterization studies and exercise tests.

The psychiatric and psychologic evaluations prior to cerebral vascular accidents revealed that these patients were adjusting in a manner in keeping with their cardiac illness. Neurologic examination at that time revealed no major signs of central nervous system deficit in the three patients in whom cerebral complications developed following commissurotomy.

In two patients undergoing commissurotomy evidence of serious neurologic involvement developed within the first two days, and in the third patient on the twelfth postoperative day. While the immediate impact of these complications resulted in pronounced neurologic deficits, follow-up studies showed gradual recovery. Of two patients with initial expressive aphasia, one retained only a mild paresis of the left arm, while the other showed some degree of residual expressive aphasia, even after three and a half years. The third patient, with initial hemiplegia, achieved almost complete recovery.

The psychologic retests indicated definite impairment associated with the occurrence of cerebral vascular accidents and a gradual recovery of psychologic functioning to the preoperative level, with minor residuals remaining in perceptual motor abilities and personality functioning after three years. Intelligence, as measured by the Wechsler-Bellevue test, indi-

cated almost complete return to the preoperative level within two years.

Psychiatrically, two of three patients with postoperative neurologic deficit made satisfactory readjustments and returned to previous occupations; while the third (with residual aphasia) had definite rehabilitation difficulties and could not return to her full-time professional job.

Improvement in cardiac dynamics following the surgery was uniformly disappointing in these three cases.

Among many factors influencing readjustment, outstanding was availability of supportive individuals in the patient's milieu and his ability to utilize them in his day-to-day rehabilitative efforts.

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Problems Associated with the Use of Antibiotics for the Prevention of Primary Episodes of Rheumatic Fever*

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CONTROL of beta hemolytic streptococcal infections stands today as the most logical approach to the prevention of rheumatic fever. If bacterial infections can be prevented or adequately treated sufficiently early, acute rheumatic episodes might be substantially reduced in number. To date, programs for such control are advised for those patients who already have suffered one or more rheumatic episodes. A number of studies have been undertaken in an attempt to control streptococcal infections prior to the initial attack of rheumatic fever. The present investigation was designed to provide data on the efficacy of penicillin therapy in streptococcal illness as well as to reduce the number of streptococcal carriers and thus prevent primary episodes of rheumatic disease. The obstacles encountered barred the successful execution of these purposes.

MATERIAL AND METHOD

One public school for white students in Miami, Florida, with 824 children registered in grades 1 through 6 (ages six through twelve years), was selected for study. Most of the children came from "middle income" families.

Every morning that school was in session from September 4, 1958, through November 30, 1958, a technician from the National Children's Cardiac Hospital visited the school and tabulated the roster of absentees, as reported daily by each of the twenty-nine teachers. The daily enrollment of the school (present plus absent) was obtained from the school secretary.

On the first day of absence, the parent of the absent child was called on the telephone to determine the reason for absence. The technician then visited the home of each child suffering from a respiratory illness, or from fever or other illness of undetermined origin. She also visited each home without a phone. These visits were made on the same day, almost always before the attending physician saw the child, and therefore before any medication had been administered. Throat cultures were taken by previously described technics,[1-3] and were returned to the laboratory, where they were streaked on plates of blood agar base (Difco®) and neopeptone infusion agar (Difco), each enriched with 4 per cent sterile defibrinated sheep's blood.† After incubation for eighteen to twenty-four hours, the plates were examined for the presence of beta hemolytic streptococci. Pure cultures of these organisms were obtained and grouped by the Lancefield technic.[4]

As soon as beta streptococci were identified positively (one to five days after swabbing), the families of these children were informed that "strep" had been recovered. They were urged to consult their physicians for further guidance and therapy, if the physicians so advised.

Repeat cultures were taken every two weeks from the throat of each child who had previously had a positive culture. This was continued until two successive cultures were negative. In the case of each positive repeat culture, either the family, the physician, or both were informed of the findings. Whenever the physician sought advice, he was informed that we recommended a single injection of 1.2 million units of Bicillin® as the treatment of choice, although oral administration of penicillin (200,000 to 250,000 units) three times a day for ten days was satisfactory.

RESULTS

During the sixty school days of this program, the average daily enrollment was 824 children,

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* From the Department of Medical Research, National Children's Cardiac Hospital, Miami, Florida.
This study was supported in part by U. S. Public Health Service Grant H-1738.

TABLE I

Results of Throat Cultures Collected During and After Ninety-Nine Episodes (in Ninety-Eight Children) of Respiratory Illness Associated with Recovery of Beta Hemolytic Streptococci, September–December 1958, Miami, Florida*

No. of Cultures Taken†	Number of Respiratory Episodes in Which:					
	Cultures Became Negative			Cultures Remained Positive		Incomplete Follow-Up
	With Treatment	Without Treatment	Unknown	With Treatment	Without Treatment	
1	...	...	...	...	...	3 (3)
2	...	...	...	2 (2)	...	5 (5)
3	9 (9)	6 (2)	19 (15)	2 (2)	7 (6)	...
4	4 (4)	...	2 (1)	4 (2)	2 (2)	...
5	6 (5)	...	1 (1)	1 (1)	5 (4)	...
6	2 (2)	2 (2)	...	4 (3)‡	2 (2)	...
7	2	...	...	3 (3)	2	...
8	...	...	...	2 (2)‡	...	...
9	1	...	...	1	...	...
Total 99 (78)	24 (20)	8 (4)	22 (17)	19 (15)	18 (14)	8 (8)

* Numbers in parentheses indicate group A beta hemolytic streptococci.
† Includes initial cultures.
‡ In one instance, a group A streptococcus was isolated initially; subsequently a group G organism was recovered.

representing 49,467 children-days. There were 1,272 children-days of absence, including 375 absences attributed to respiratory illness. Refusals to participate in the program occurred only thirty-one times, and throat cultures were collected in 344 cases during illnesses. When an illness lasted more than one day, the culture was taken the first day only.

Positive Cultures: Beta hemolytic streptococci were recovered during ninety-nine episodes of respiratory infection from the throats of ninety-eight children; seventy-eight were group A organisms.

Repeat throat cultures taken on the ninety-eight children showed that almost all the children continued to harbor streptococci in their throat for many weeks if they were untreated. Among the treated children, many continued to carry the organisms for long periods of time.

Table I lists the results observed in each child from whom throat culture was taken because of respiratory illness causing absence from school, and who was found to harbor beta hemolytic streptococci. Of ninety-nine episodes of absence, eight were not studied completely. Of the remaining ninety-one, fifty-four were found to have two successive negative cultures, while thirty-seven still were harboring beta streptococci when the project terminated because of Christmas recess. Seventy-eight episodes were associated with group A organisms; eight were incomplete, forty-one became negative on follow-up and twenty-nine continued to yield beta streptococci.

Effect of Treatment: Data on treatment were obtained verbally from parents or physicians. Parents were unable to give information as to the specific drug used and physicians were reluctant to spend the time necessary to consult their records to provide definite dosage schedules. Many physicians advised parents that no treatment was indicated; others prescribed broad spectrum antibiotics (erythromycin, tetracycline, Terramycin®) and/or sulfa drugs, Kynex® or Combiotic.® Still others gave penicillin, orally or intramuscularly, almost always in doses far below the recommended ten-day coverage. Estimate of the adequacy of therapy could be judged only rarely and therefore is not included. A number of doctors consulted directly with us and then prescribed adequate doses of penicillin. Because throat cultures were taken on the first day of illness, no therapy had been administered prior to the initial culture. However, more than half the children received some form of antibiotic agent before the subsequent cultures were taken.

The numbers of colonies of beta hemolytic

TABLE II

Number of Beta Hemolytic Streptococcal Colonies Observed during Ninety-Nine Episodes (in Ninety-Eight Children) of Respiratory Illness, September–December 1958, Miami, Florida*

No. of Colonies	Number of Respiratory Episodes in Which:					
	Cultures Became Negative			Cultures Remained Positive		Incomplete Follow-Up
	With Treatment	Without Treatment	Unknown	With Treatment	Without Treatment	
0–9	2 (2)	4 (1)	5 (3)	1	3 (3)	2 (2)
10–24	2 (2)	1	4 (4)	3 (3)	4 (3)	1 (1)
25–99	3 (3)	2 (2)	7 (5)	4 (3)	2	1 (1)
100–999	5 (4)	...	...	3 (2)	2 (2)	2 (2)
1,000+	12 (9)	1 (1)	6 (5)	8 (7)	7 (6)	2 (2)
Total 99 (78)	24 (20)	8 (4)	22 (17)	19 (15)	18 (14)	8 (8)

* Numbers in parentheses indicate group A beta hemolytic streptococci.

streptococci in each episode of respiratory illness are shown in Table II. Almost 50 per cent of the children harbored 100 or more colonies, whether or not their throats showed subsequent clearing. It was also noted that forty of seventy-eight episodes were associated with more than 100 colonies of group A organisms.

The duration of follow-up varied with three factors: (1) availability of the child to continue in the study; (2) promptness with which two successive negative cultures were obtained; and (3) date of isolation of initial positive culture. Thus, the follow up varied from two weeks to three and one-half months.

Rheumatic fever or glomerulonephritis did not occur in any of the ninety-eight children who were found to harbor beta streptococci.

COMMENTS

Prevention of primary or initial attacks of rheumatic fever by eradication of streptococcal carriers is an intriguing approach for both public health officers and practicing physicians. However, today, such a program presents tremendous problems.

(*1*) *Cost:* The project, as carried out, required the services of two and one-half technicians for the one school surveyed, a school with an enrollment of 824 children. Based on a minimum annual salary of $3,600 per technician, the cost of technical help alone was approximately $10 per child enrolled in the school. To this cost must be added the costs for laboratory space, bacteriologic supplies and equipment, transportation and remuneration to the physician supervising the program. To improve the project, studies on blood should have been made. This, too, would have increased costs.

Approximately 20 million children between the ages of six and twelve years attend public schools in the United States. A reasonable estimate of the cost of this program on a national basis is half a billion dollars annually.

(*2*) *Cooperation of Parents:* Almost all families contacted in our study participated willingly; only a few refused to permit taking of throat cultures. However, even after they were notified that their children carried streptococci, many parents neglected to communicate with their physicians.

(*3*) *Physicians:* A substantial number of physicians thought that treatment of children carrying streptococci was not indicated. Although throat cultures were taken when children were sufficiently ill to be absent from school, by the time the results of the culture were available the children usually were clinically well and back in school. Other physicians prescribed a variety of medications, many of which were bacteriostatic rather than bactericidal. Occasionally a physician refused to administer penicillin because of his fear of sensitivity reactions.

(*4*) *Therapy:* Most physicians appreciated the value of penicillin administration in treating streptococcal illness. However, doses were frequently inadequate or were not adminis-

tered for a ten-day period. When penicillin was administered orally, even in adequate daily dosage over a ten-day period, many throats still were found harboring streptococci when repeated cultures were carried out two weeks later.

(*5*) *Technics:* Although streptococcal bacteriology has been a major activity of the research laboratory of the National Children's Cardiac Hospital since 1952, certain difficulties in obtaining accurate data on the incidence and prevalence of these organisms appear insurmountable. Refinements in procedures to increase the accuracy of streptococcal recovery are essential, and are currently under investigation. Another technical problem is the delay in obtaining findings because of the cultural requirements for definite identification of the presence of beta hemolytic streptococci. Faster identification of beta streptococci and classification into their specific groups may be possible in the future, when fluorescent microscopic technics are perfected.

(*6*) *Communication:* A problem encountered during the investigation was the difficulty of conveying information to people who did not have a telephone. A second obstacle to an adequate and effective program was the lag in time between illness and positive identification of streptococci necessary before the family could be notified. Another difficulty lay in the inadequacy of obtaining satisfactory data on medical treatment administered, and of educating physicians sufficiently to ensure proper and sufficient therapy.

(*7*) *Poverty:* In some instances, parents stated they could do nothing for the care of their children because of lack of funds to pay for medical care and antibiotics. Many communities provide free care, but other areas have inadequate means for such care or fail to disseminate knowledge of the availability of this service.

Summary

Based on the concept that the prevention of rheumatic fever can be attained by the early eradication of infection with the group A beta hemolytic streptococcus, the current program was devised to help evaluate its efficacy in the prevention of initial attacks of rheumatic disease. In a school with an average daily enrollment of 824, each absent child had his throat swabbed on the initial day of absence if the illness was of respiratory origin. On identification of beta hemolytic streptococci in the throat culture, the family and/or physician was notified, and antistreptococcal treatment was suggested.

The investigation revealed that such an attempt to prevent rheumatic fever (1) was prohibitively costly; (2) encountered obstacles in obtaining cooperation from the lay public; (3) indicated lack of uniformity in attitude to therapy by different physicians; (4) demonstrated problems in bacteriologic technics; (5) posed difficulties in communication; and (6) ran the risk of inaccurate statistical appraisal.

Because of the difficulties encountered, we believe any program of prevention of primary attacks of rheumatic fever by use of antibiotics is impractical on a community service basis and at the present time should be reserved for research only.

Although primary attacks of rheumatic fever cannot yet be handled as a community-wide project, the secondary prevention program, as advocated by the American Heart Association,[5] is strongly urged, especially for those areas where rheumatic fever is known to occur frequently. According to this program, all known persons who have had one or more attacks of rheumatic fever should receive prophylactic antibiotic therapy indefinitely.

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Coronary Nodal Rhythm*

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CORONARY nodal rhythm is a cardiac abnormality characterized by accelerated atrioventricular activation. The P-R interval is 0.10 second or less, well within the range of the A-V nodal rhythms, but the P waves are upright in both leads I and II; QRS complexes are normal (Fig. 1). As a matter of definition, coronary nodal rhythm must be distinguished from *coronary sinus rhythm*, which is characterized by a *normal* P-R interval and retrograde (inverted) P waves in leads II and III. Katz[1] found coronary nodal rhythm in 172 (0.3 per cent) of 50,000 patients. Its incidence was at least three times greater among patients admitted to the Lemuel Shattuck Hospital during 1958. Twelve cases were identified, representing about 1 per cent of all patients having electrocardiograms in that year. A review of these patients disclosed certain noteworthy features.

The diagnostic requirement of upright P in leads I and II permits considerable leeway in terms of electrocardiographic patterns, since these P waves can vary in amplitude and P in lead III may be upright, diphasic, flat or inverted. Direction of the P wave is perhaps more comprehensively stated in vector terms. The mean frontal P vector (P axis) in coronary nodal rhythm lies between −29 and +89 degrees on the axial reference system. This range includes the normal P vector orientation (+45 to +65 degrees)[2,3] and a zone on either side of it (Fig. 2).

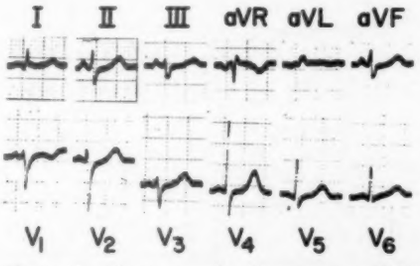

FIG. 1. Case 10. An example of coronary nodal rhythm in an electrocardiogram which is otherwise virtually within normal limits. The P-R interval is 0.10 second, the P waves are upright in leads II and III as well as in lead I. The P wave axis is +70 degrees.

CLINICAL AND ELECTROCARDIOGRAPHIC FEATURES

Table I lists our patients in order of increasing P axis (from "left" to "right" by convention). The data may be summarized as follows:

(1) The P axes ranged from − 10 to +70 degrees. Half (Cases 7 to 12) were virtually normal (+50 to +70 degrees) with upright P waves in lead III as well as in leads I and II.

(2) There was no association between coronary nodal rhythm and any range of heart rate, blood pressure or QRS axis.

(3) Only two of the electrocardiograms were otherwise within normal limits. The ten abnormal tracings showed T wave abnormalities, three of which suggested hypokalemia. Only one of these patients actually had a low serum potassium level.

(4) Two patients were receiving digitalis.

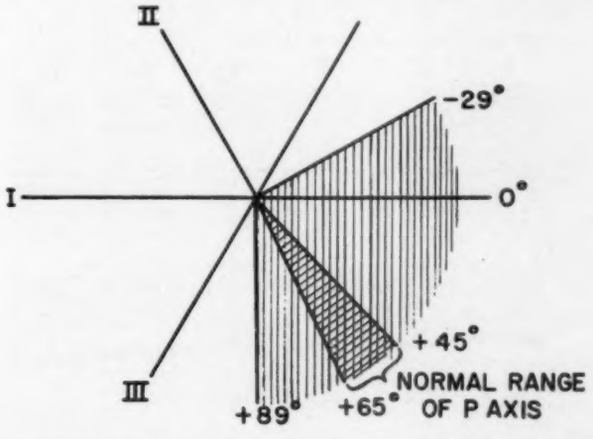

FIG. 2. Standard axial reference system with range of P axes indicated for normal persons and for electrocardiograms satisfying criteria for coronary nodal rhythm.

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TABLE I
Data in Twelve Patients with Coronary Nodal Rhythm at the Lemuel Shattuck Hospital, 1958

Case No., Sex and Age (yr.)	P-R Interval (sec.)	P Axis (degrees)	QRS Axis (degrees)	Heart Rate (per minute)	Digitalis	Blood Pressure (mm. Hg)	Other Electrocardiographic Diagnoses	Clinical Diagnoses	Serum Potassium (mEq./L.)
1, F, 49	0.10	−10	+30	86	No	98/60	Hypokalemia	Cerebrovascular accident, alcoholism	4.5
2, F, 58	0.10	+10	0	94	No	190/100	Non-specific T wave abnormality	Cerebrovascular accident, hypertension, duodenal ulcer	...
3, F, 42	0.09	+30	+30	96	No	110/70	Hypokalemia	Cirrhosis	4.1
4, F, 71	0.10	+30	−20	94	No	114/70	Left ventricular hypertrophy	Tuberculosis (spine), duodenal ulcer	...
5, F, 65	0.09	+30	0	68	Yes	140/70	Digitalis effect	Rheumatoid arthritis	4.2
6, F, 70	0.10	+30	+20	54	No	185/100	Left ventricular hypertrophy	Cerebrovascular accident, hypertension	5.1
7, F, 66	0.09	+50	−40	128	No	110/70	Non-specific T wave abnormality	Carcinoma of lung	...
8, F, 68	0.10	+50	+20	68	No	140/85	Within normal limits	Carcinoma of breast	...
9, F, 50	0.10	+60	+60	102	No	130/80	Non-specific T wave abnormality	Tuberculosis (lung), carcinoma of breast	4.5
10, F, 42	0.10	+70	*	86	No	118/70	Within normal limits	Bronchiectasis	5.3
11, M, 59	0.09	+70	+80	130	Yes	132/78	Atrial enlargement; non-specific T wave abnormality	Carcinoma of lung	...
12, F, 54	0.08	+70	+40	113	No	180/90	Hypokalemia	Cirrhosis, emphysema	3.6

* QRS axis in this patient was indeterminate in the frontal plane leads because of equal positive and negative amplitude.

This had no effect upon coronary nodal rhythm in one of these in whom an earlier electrocardiogram was available (Fig. 3).

(5) The patients' diseases and ages were characteristic of the hospital population. Five of the six with more normally oriented P axes had diffuse diseases of the lung.

(6) Eleven of the twelve patients were women.

Two patients reverted to sinus rhythm with a normal P-R interval. In each case the frontal P axis moved 30 degrees to the right of its orientation during coronary nodal rhythm. The QRS axes were unchanged (Fig. 4).

COMMENTS

Some shortening of atrioventricular conduction time has been described in hyperthyroidism,[4] anxiety states,[5] paroxysmal tachycardia,[6] schizophrenia,[7,8] welding gas poisoning[4] and atrial infarction.[9] In such cases the P-R interval usually exceeded 0.10 second. Furthermore, none of these conditions was recognized in our patients. The fact that eleven

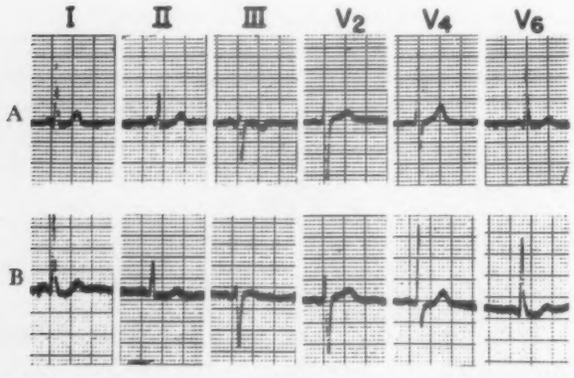

FIG. 3. Case 5. A, coronary nodal rhythm in a sixty-five year old woman with rheumatoid arthritis. The P-R interval is 0.09 second and the P axis is +30 degrees. B, same patient receiving full doses of digitalis two weeks later. The previously normal electrocardiogram (apart from coronary nodal rhythm) now shows effect of digitalis but no change in pacemaker.

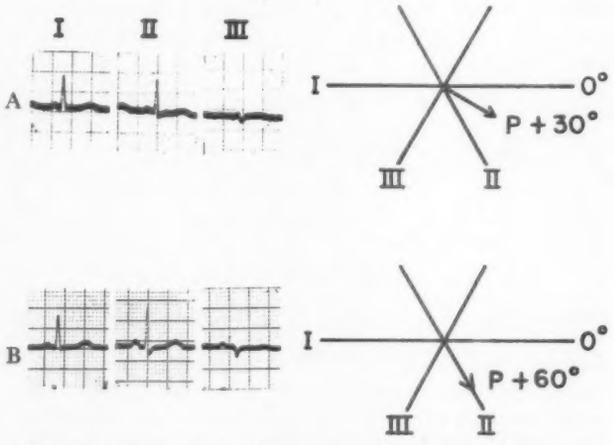

FIG. 4. Case 3. Spontaneous reversion from coronary nodal rhythm to sinus mechanism. The P axis has shifted from +30 degrees (A) to +60 degrees (B). T waves are slightly less abnormal in (B). P-R intervals: A, 0.08; B, 0.13 second.

of the twelve patients were women is of interest in view of the preponderance of women among persons with paroxysmal tachycardia and relatively short P-R intervals.[6] Two of our patients had had palpitations related to physical or emotional stress but these could not qualify as examples of "spontaneous" paroxysmal rapid heart action. Carotid sinus stimulation in two patients (Cases 4 and 12) slowed the heart but did not affect the P-R interval or P axis.

Coronary nodal rhythm is named for the probable site of its pacemaker—the upper A-V node at the mouth of the coronary sinus. Its location near the "tail" of the sinus node[1] may account for the relatively horizontal P axes in several patients (Cases 1 to 6). This is indicated by the P axis shifts in two patients (Cases 2 and 3) upon reversion to sinus rhythm (Fig. 4) which would be expected if the pacemaker moved from a lower to a higher position.

The more normal P axes (upright P in leads I, II and III) in the other patients (Cases 7 to 12) could have resulted from accelerated atrioventricular conduction with a normal sinus pacemaker. However, diffuse pulmonary disease is associated with verticality of the P axis[2,3] so that normal intra-atrial conduction cannot be taken for granted in at least five of these six cases. One patient (Case 11) had tall P waves suggesting atrial enlargement. Furthermore, rhythms originating in or near the A-V node can produce vertical P axes. Impulses arising from the region of the A-V node can initially travel up the interatrial septum[10] before "showering" down over the atria to produce upright P waves in leads I, II and III.

The significance of coronary nodal rhythm is not clear. Each patient had a serious systemic illness, but this was typical of the entire patient population. In regard to the advanced age in the majority, it is of interest that the P-R interval normally increases with age.[5]

Summary

Twelve cases of coronary nodal rhythm are reported. Eleven patients were women. The administration of digitalis to one patient did not influence atrioventricular conduction, which was also unchanged by effective vagal stimulation in two others. Six patients had leftward deviation of the P axis. Two of these reverted to sinus rhythm with a corresponding change in the P vector. Six others, five of whom had pulmonary disease, had P axes which were either normal or slightly oriented to the right. Separate mechanisms may explain coronary nodal rhythm in each group.

Acknowledgment

We wish to express our appreciation to Mrs. Constance Dorr for technical assistance and collaboration.

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Lipid Measurements in Coronary Artery Disease

Comparison with an Age-Matched Normal Control Group*

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GENERAL agreement exists that in the majority of patients who have had a myocardial infarction some abnormality in the serum lipid can be demonstrated. However, there is disagreement as to which lipid measurement most effectively separates normal persons from those with coronary disease. This study compared 104 male survivors of acute myocardial infarction and ninety-one age-matched clinically normal men in terms of total serum cholesterol, total "stainable lipid" and the electrophoretically determined distribution of lipoprotein as measured by oil red O staining.

MATERIAL AND METHODS

All patients ranged in age from thirty to sixty years and the data are reported in the thirty to forty, forty-one to fifty and fifty-one to sixty year categories. The 104 patients with myocardial infarction were hospitalized at the Veterans Administration Center in the past four years. To have as homogeneous a group as possible, patients with hypertension, diabetes or other endocrinopathy, gross cardiac failure, kidney disease or known familial lipid disorders were eliminated. Measurements reported are those made at least two months after the infarction, since we have noted a remarkable fluctuation of the serum cholesterol levels in many patients in the early postinfarction period (Table 1). Fluctuations in serum cholesterol levels over many months, as well as the laboratory reproducibility, have been reported.[1] The ninety-one control subjects were normal in terms of complete history, physical examination and resting electrocardiogram. These persons were interested physicians, patients who were examined for "check-ups" and patients who entered the hospital for elective surgery for hemorrhoids or a hernia, or for psychiatric reasons. So far as could be determined, their diets were similar to the group of patients with coronary disease.

All laboratory measurements are reported as the means of four or more determinations, carried out on different days, in the postabsorptive state. Total serum cholesterol was performed by the method of Kingsley.[2] In our experience this technic gives results ranging up to 10 per cent higher than the method of Abell.

The method of Jencks and Durrum[3] was used for paper electrophoresis, staining and elution of the lipoproteins. Results are reported as total stainable lipid units as measured in the Beckman D-U Spectro-

TABLE 1

Serum Cholesterol Levels Within the First Three Months After Myocardial Infarction*

Case No.	48 Hours	2 Weeks	4 Weeks	6 Weeks	12 Weeks
1	205	214	332	191	...
2	261	323	...	395	345
3	163	174	208	304	360
4	175	148	177	214	235
5	198	227	307	260	256
6	99	192	250	206	188
7	149	211	...	191	200
8	166	...	...	275	277
9	218	...	305	265	282
10	269	...	310	320	297
11	408	...	338	388	350
12	267	...	368	...	320
13	231	...	251	...	253
14	375	...	285	...	278
15	280	...	328	...	308
16	350	261	299	277	284
17	319	...	368	...	363

* All figures are in mg. per cent.

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This study was supported in part by a grant-in-aid from G. D. Searle & Co., Chicago, Illinois.

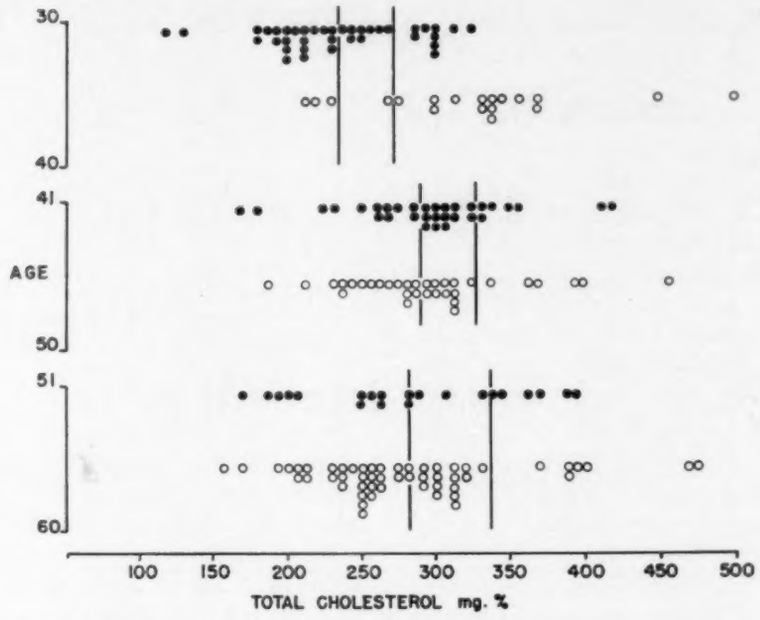

FIG. 1. Total cholesterol levels of patients with myocardial infarction (○) and matched control subjects (●). Vertical line to the left represents mean of the normal subjects in each age group; vertical line to the right represents one standard deviation from the mean. Abnormalities read left to right.

photometer, and as per cent alpha to beta stainable lipid ratio. In another paper[4] we have indicated the reproducibility of these measurements and the dye uptake of the individual lipid components. Sterol ester and triglyceride account for most of the staining. Phospholipid stains weakly and free cholesterol and carotene do not stain at all. In this paper we have also depicted the good correlation between per cent beta-cholesterol (a commonly used parameter) and per cent beta stainable lipid. Variability noted is due to the triglyceride represented in the stain. This study also shows that alpha-lipoprotein is, for practical purposes, identical with dense lipoprotein, or S_f less than 0. Beta, considered as the band from the point of origin to the sharp advance border, includes all the light material from S_f 0 through the chylomicrons.

RESULTS

Figures 1, 2 and 3 are the "scattergrams" of the normal subjects and patients with coronary disease for total cholesterol, total stainable lipid and alpha/beta stainable lipid ratio. The first vertical line on the left in Figures 1 and 3 represents the mean of the normal subjects in that decade, while the second vertical line to the right represents 1 standard deviation from the mean. In Figure 2 the order is reversed so that the line on the right is the mean, the line to the left is 1 standard deviation from the mean, and abnormalities read right to left. On this basis, the normal cholesterol value ranges to a maximum of 270 mg. per cent in the thirty to forty year age group; to 329 mg. per cent in the forty-one to fifty year category and to 338 mg. per cent in the fifty-one to sixty year age group. The alpha/beta minimum normal ratios are: 20 per cent, ages thirty to forty years; 16 per cent, ages forty-one to fifty years; and 19 per cent, ages fifty-one to sixty years. The total lipid stain units are plotted in only two age categories, thirty to forty years and forty-one to sixty years, since no differences appeared between the older groups. Maximum normal at ages thirty to forty years is 55 units; at ages forty-one to sixty years, 63 units.

It can be seen that in the younger age groups, all three of these measurements effectively separate the coronary patient from the clinically normal person. Statistically, p is less than 0.001 in each measurement as determined by the rank sum test. However, examination of the graphs of the forty-one to fifty years and fifty-one to sixty year age categories will show that total cholesterol and total stainable lipid measurements are not substantially different in the groups with coronary disease as compared to the normal subjects. Statistical analysis also fails to show significant difference.

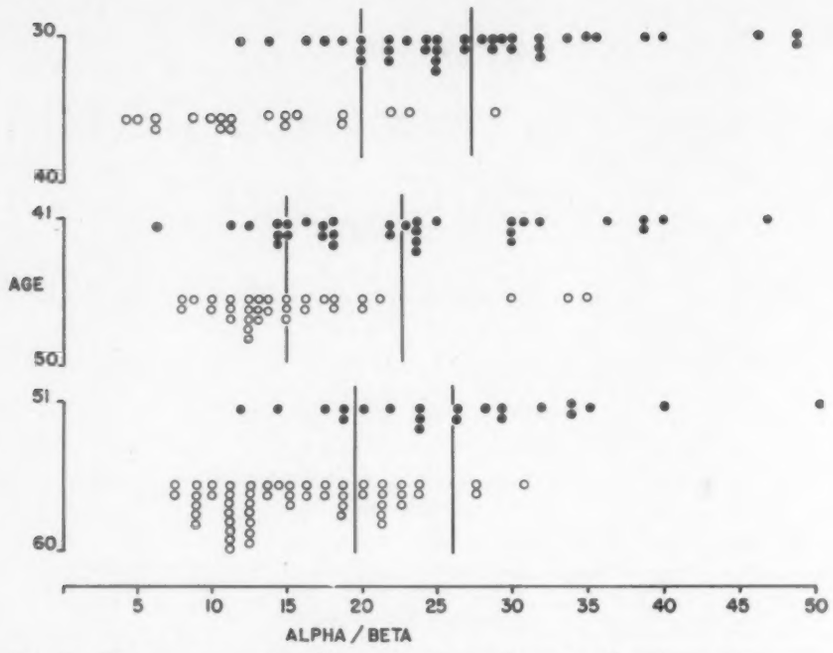

FIG. 2. The per cent alpha/beta oil red 0 stain units of patients with myocardial infarction (○) and matched control subjects (●). Vertical line to the right represents the mean of normal subjects in each age group; vertical line to the left represents one standard deviation from the mean. Abnormalities read right to left.

The alpha/beta stainable lipid ratio even in the older decades clearly shows that most patients with coronary disease fall outside the normal range ($p < 0.001$). Figure 4 depicts the percentage of patients with abnormalities in all age groups and shows that while 72 per cent of the 104 patients with coronary disease had some abnormality of serum lipid, this figure would have been reduced to 30 per cent if serum cholesterol were the only measurement performed.

COMMENTS

Many investigators have submitted evidence to show that one lipid estimation discriminates best between normal persons and those with

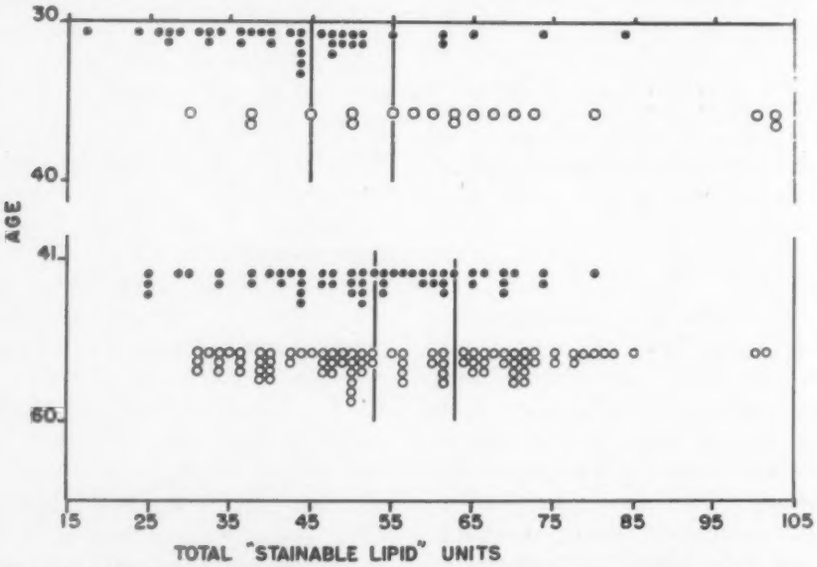

FIG. 3. Total "stainable lipid" in patients with myocardial infarction (○) and matched control subjects (●). Vertical line to the left represents mean of normal subjects in age group depicted; vertical line to the right represents one standard deviation from the mean. Abnormalities read left to right.

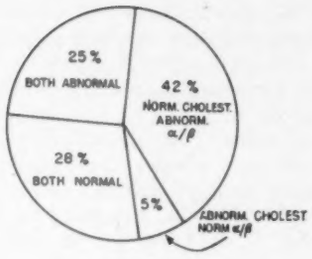

FIG. 4. Percentage of abnormalities of blood lipid in 104 men surviving a myocardial infarction.

coronary disease. Albrink and Man[5] report that serum triglycerides are abnormal in 85 per cent of patients with myocardial infarction. Lawry and co-workers[6] conclude that neither cholesterol, S_f 12–20, S_f 20–100, nor any combination showed clear superiority in discriminating between patients with coronary disease and normal persons. They further suggest that the cholesterol measurement is the most practicable. Schlessinger et al.,[7] working with a small group of twenty-four patients with coronary disease, prefer to use the S_f 0–400 and atherogenic index measurements. Gofman and associates[8] have a large amount of data to support this point of view. Orvis,[9] Nikkila[10] and Brunner[11] have presented evidence that beta-lipoprotein cholesterol is the most satisfactory determination. Jencks and colleagues[12] find electrophoresis and staining methods to be superior to S_f 12–20 measurement or total serum cholesterol. Likoff et al.[13] indicate an advantage for radioactive fat absorption studies. The most recent report of Mattingly et al.[14] concludes that serum cholesterol is as informative as the more complicated ultracentrifuge measurements. Their data indicate that the serum cholesterol of the younger patient with coronary disease is most different from the normal person while the differences become much less with advancing age. This same trend can be observed in most of the studies reported and is also quite obvious in our own experience.

Not enough attention has been paid to the age factor in determining lipid values in normal persons versus those with coronary disease. Any of the measurements commonly in use will segregate the coronary patient under forty years of age. If it is true that the level of serum cholesterol multiplied by time elapsed equals propensity for atherosclerosis, then one would expect that those who are the youngest would have the highest cholesterol levels. If the maximum normal cholesterol value of 270 mg. per cent for the age group under forty years is used, then the majority of patients with coronary disease over forty years of age would fall above this level. The same would be true of most of the clinically normal people in the older age groups. The chief advantage of the alpha/beta ratio lies in the fact that in normal persons it does not change greatly with aging.

On the basis of the experiences of the Korean war[15] there is little doubt that clinically normal people may have advanced coronary artery disease. In our series, as in others, the term "normal control" is a tenuous one and really means clinically normal and not yet manifesting overt atherosclerosis. The usefulness of any lipid parameter as a predictor of a future myocardial infarction is, of course, the key issue. The Framingham study[16] indicates that a cholesterol value above 260 mg. per cent constitutes definite added risk of coronary disease. The predictive value of alpha/beta lipoprotein ratios is currently under study.

SUMMARY

One hundred four male survivors of acute myocardial infarction and ninety-one age-matched clinically normal men were studied.

Measurements of total cholesterol, total stainable lipid and the ratio of alpha/beta stainable lipid were made. Below the age of forty years, all of these effectively discriminated the normal persons from those with coronary disease. The alpha/beta ratio provided the best segregation of the groups above the age of forty years.

Cholesterol measurements made within the first two months after myocardial infarction are rapidly fluctuating and cannot be used as indicators of the true or "steady state" cholesterol level.

The technic of electrophoresis and staining of lipoproteins is reproducible, reasonably simple, inexpensive and adaptable for large scale studies.

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Experimental Studies

Ventriculo-Ventricular Dissociation*

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Electrical dissociation between the right and the left atrium has been reported by several authors. Uniatrial fibrillation,[1,2] uniatrial flutter,[3] fibrilloflutter[4] and other forms of dissociation have been described.

In 1921, Kisch[5] was the first to report a difference in the configuration and frequency of the fibrillary waves obtained by means of direct epicardiac leads from the two ventricles. This was confirmed by others. Sodi-Pallares and co-workers[6] pointed out the existence of a "physiological barrier" in the septal mass between the two ventricles. Similar observations concerning the ventricles have been made in our laboratory during open chest experiments in dogs.

Material and Method

Forty-seven dogs, weighing 8 to 22 kg., were anesthetized by intravenous administration of sodium pentothal (15 mg. per kg.). Under intratracheal administration of oxygen the thorax was opened and the pericardium was incised. Ventricular fibrillation was induced either by administration of adrenaline (10 to 15 mg. intracardially) or by electric shock (7 to 8 amperes, 150 to 170 volts for 0.7 to 1 second).

Before inducing ventricular fibrillation and immediately following it, direct epicardiac leads were recorded on a two-channel direct-writing electrocardiograph. The thread electrodes were applied in the middle between the base and the apex of each ventricle. The entire surface of each of the two ventricles was carefully explored in those instances in which a difference was noted in the tracings so obtained.

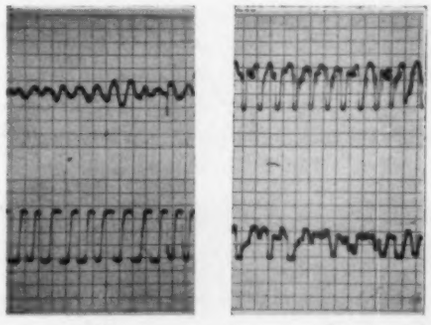
Results

In fourteen of the forty-seven dogs (29 per cent) a difference in the electrical activity between the two ventricles was noted. In five of these fourteen adrenaline had been administered and in the other nine electrical shock was used. The onset of the dissociated activity began from one to sixteen minutes after the attempt to fibrillate the ventricles and lasted from one-half to three minutes (average one and a half minutes) until the electrical activity became uniform for both ventricles.

The differences in the electrical activity between the two ventricles were classified into four groups as follows:

Group I. Fibrillation and Flutter: In this group of eight animals, one of the ventricles was fibrillating while the other showed flutter waves (Fig. 1A). The frequency of the fibrillary waves was from 210 to 500 per minute for the right ventricle and from 225 to 550 per minute for the left ventricle. The frequency of the flutter waves was from 215 to 400 per minute for the right ventricle and from 125 to 450 per minute for the left ventricle.

Group II. Fibrillation and Idioventricular Rhythm: This type of dissociation was noted in two dogs. In these the ventricles showed ventricular tachycardia at a rate of approximately 200 per



A B

Fig. 1. A, *upper tracing*, right ventricle in fibrillation; *lower tracing*, left ventricle showing flutter waves. B, *upper tracing*, left ventricle showing ventricular tachycardia; *lower tracing*, right ventricle in fibrillation.

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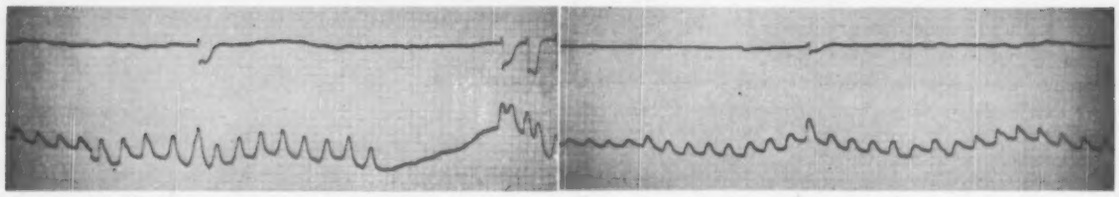

FIG. 2. Standstill and ventricular tachycardia in two animals. *Upper tracing*, right ventricle in arrest with occasional complexes which appear to be due to electrical impulses transmitted from the opposite ventricle. *Lower tracing*, left ventricle showing a rhythmic activity with the characteristics of ventricular tachycardia.

minute while the other ventricle was fibrillating (Fig. 1B).

Group III. Standstill and Ventricular Tachycardia: This type of dissociated electrical activity was noted also in two animals. The left ventricle displayed ventricular tachycardia at a rate of approximately 150 per minute while the right ventricle, in arrest, showed occasional complexes which appeared to be due to electrical impulses transmitted from the opposite ventricle (Fig. 2).

Group IV. Idioventricular Tachycardia of Different Frequencies: In this type of dissociation, noted in two dogs, one of the ventricles showed a very slow idioventricular rhythm with periods of arrest and the other ventricle displayed a faster and perfectly regular idioventricular rhythm with a wide and bizarre ventricular complex. The idioventricular activity was independent for each of the ventricles (Fig. 3).

COMMENTS

The results reported in this paper suggest the possibility of electrical independence of the two ventricles. This phenomenon could be called ventriculo-ventricular dissociation. Kisch[5] reported a difference in the configuration of the fibrillary waves obtained by means of direct epicardiac leads from the two ventricles. In our study a wide variety of independent ventricular rhythms was observed. Our data seem to confirm the observation of Sodi-Pallares[6] in an indirect way.

Further investigation is needed to find out if the dissociation observed in these experiments is a transient state only in the heart of a dying organism. In this case a difference in the rhythm could be explained as due to the different degree or rapidity of exhaustion of the ventricles or to the different degree of involvement by a "circus movement" instigated at one or more points and progressively spreading to larger masses of the ventricular myocardium.

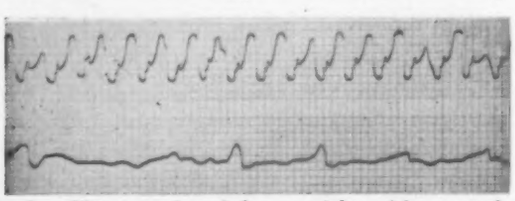

FIG. 3. *Upper tracing*, left ventricle with a perfectly regular idioventricular rhythm with a wide and bizarre ventricular complex. *Lower tracing*, right ventricle with an independent slow idioventricular rhythm and periods of cardiac arrest.

In the present era of open heart surgery, a systematic search of suitable cases at the operating table could offer valuable material for further study of ventriculo-ventricular dissociation.

SUMMARY

In open chest experiments in forty-seven dogs, the electrical activity of the two ventricles was studied by means of simultaneously recorded epicardiac leads.

In fourteen dogs, four types of ventriculo-ventricular dissociation were observed, namely, fibrillation and flutter; fibrillation and idioventricular rhythm; standstill and ventricular tachycardia; and idioventricular tachycardia of different frequency.

Further investigation is necessary for a better understanding and explanation of our observations.

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The Influence of Quinidine and Procaine Amide on Myocardial Contractility in Vivo*

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PREVIOUS experimental studies on the possible inotropic effects of the classic antiarrhythmic agents, quinidine and procaine amide, have been limited to indirect approaches or tests utilizing *in vitro* preparations. This is in contrast with the extensive clinical use of these drugs under conditions in which a depression of myocardial contractility (negative inotropic effect) may constitute a serious side effect.

Numerous statements in the literature[1–4] are to the effect that quinidine depresses contractility while procaine amide is devoid of such activity.[2,5,6,7] Some of the early workers[8,9] drew conclusions from experiments performed with a Marey-tambour system which measures gross changes in heart volume. More recent work[3,6,7] is based on isolated preparations and may not apply directly to intact animals. In man, Starr et al.[4] found a reduction in stroke volume following large doses of quinidine. Similarly, McClendon et al.[10] concluded that procaine amide has a myocardial depressant effect. By contrast, Ferrer et al.[11] reported no changes in cardiac output following administration of quinidine. In general, these indirect tests cannot serve as a measure of contractility.[12]

The myocardial strain gauge arch, developed by Boniface, Brodie and Walton,[13] permits the direct measurement of the tension developed between two points on the left ventricle. The recorded curves of myocardial tension during systole serve at present as the most direct measure of myocardial contractility.

In the experiments reported herein, direct measurements of myocardial tension were made in anesthetized dogs before, during and after administration of quinidine or procaine amide.

MATERIAL AND METHODS

Mongrel dogs weighing from 7.5 to 13.6 kg. were anesthetized with intraperitoneal injections of sodium pentobarbital (33 mg. per kg.). Blood pressures were obtained through a mercury manometer connected to the right carotid artery. The left jugular vein was cannulated for purposes of drug infusions or injections. Under positive pressure artificial respiration a left fourth intercostal thoracotomy was performed, the pericardial sac opened and a strain gauge arch[13] sutured to the left ventricular wall. The sutures were placed deep enough and sufficient stretch was applied to the underlying myocardium to eliminate the possible effects of changes in heart size.[14,15] Subsequently, the chest was closed, the pneumothorax reduced and the animals were allowed to breathe spontaneously before control measurements were made. A few animals were kept under continuous artificial respiration after closure of the chest.

Contractile force and electrocardiograms (lead II) were registered simultaneously on a Sanborn two-channel recorder. Heart rates and P-R, QRS and Q-T intervals were measured from the electrocardiogram. The strain gauge arch connected to the amplifier-recorder system was calibrated in this laboratory using known weights. The calibration curve was linear in the range of 10 to 200 gm. In the recorded tension curves the calibration was set so that 1 gm. of tension produced a 1 mm. deflection.

All doses of quinidine gluconate were injected intravenously at a slow rate (five to ten minutes). In experiments with infusions, quinidine sulfate was employed. No differences were observed. Doses are expressed in terms of quinidine base unless otherwise indicated. All solutions and dilutions were made with normal saline. Solutions of pro-

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This work was supported by grants from the American Heart Association and the Massachusetts Heart Association.
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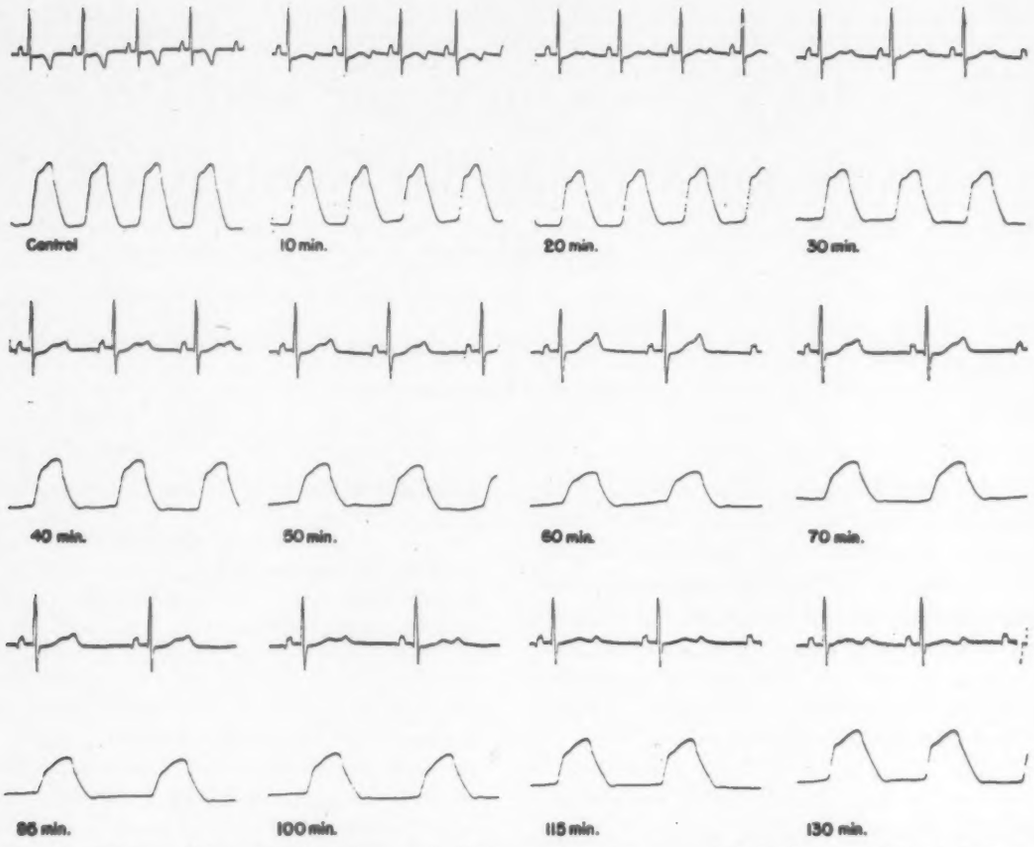

FIG. 1. Myocardial tension tracings and electrocardiograms recorded during quinidine infusions at the rate of 0.8 mg. per kg. per minute. Infusion stopped at sixty minutes.

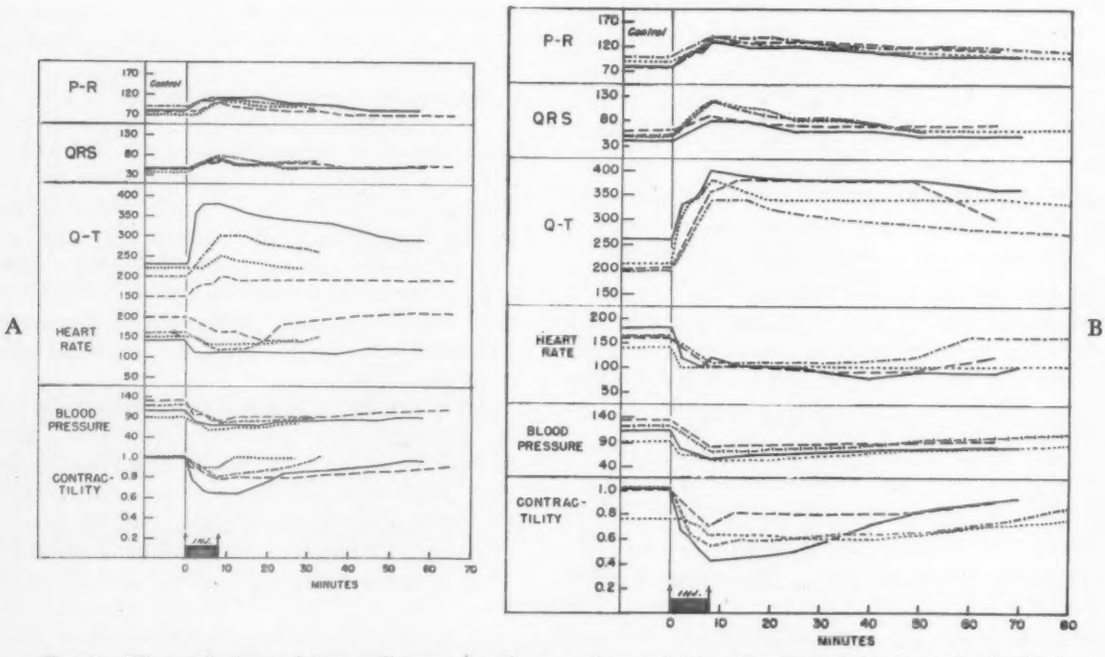

FIG. 2. Time relations of the cardiovascular changes observed following single injections of quinidine in eight dogs. A, 30 mg. per kg. of the gluconate. B, 50 mg. per kg. of the gluconate.

TABLE I
Negative Inotropic Effect of Quinidine Infusions

Total Dose (mg. per kg.)	Contractile Force	
	gm.	Treated/ Control
Dog. No. 1. Infusion rate 0.4 mg. per kg. per minute		
0	30*	1.00
6	30	1.00
12	30	1.00
20	29	0.97
28†	20†	0.67†
Dog. No. 2. Infusion rate 0.8 mg. per kg. per minute		
0	27*	1.00
6	24	0.90
15	23	0.85
20	21	0.77
36	16	0.59
48†	13†	0.48†
Dog No. 3. Infusion rate 1.6 mg. per kg. per minute		
0	38*	1.00
6	32	0.84
16	30	0.79
24	26	0.68
32	24	0.63
42	22	0.58
48†	18†	0.47†

NOTE: Doses given as quinidine base.
* Control.
† Total dose infused or maximum effect observed.

caine amide hydrochloride were freshly made from the powder product.*

RESULTS

Quinidine: Infusions of quinidine sulfate at a constant rate were made in several dogs to establish a rough range of dosages over which definite inotropic effects were seen. The rates of infusion varied in different animals from 0.4 to 1.6 mg. per kg. per minute. An experimental record of a dog infused at a rate of 0.8 mg. per minute is shown in Figure 1. A negative inotropic effect is apparent. In this case the infusion was stopped at sixty minutes and a partial recovery was observed over the next hour. In general, when the peak contractile force was reduced by less than 50 per cent of its control value, a slow but definite recovery followed when the drug was discontinued. A reduction

* E. R. Squibb & Sons, New York, New York.

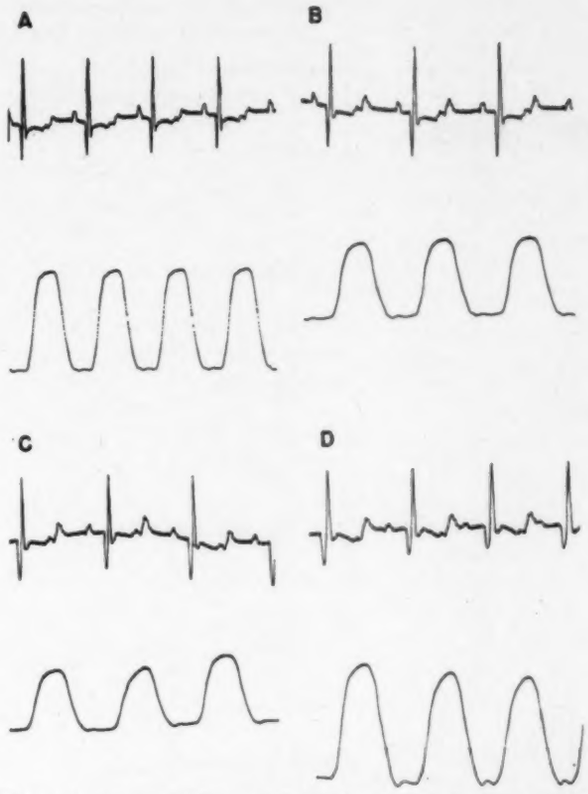

FIG. 3. Myocardial tension tracings and electrocardiograms taken before (A), three minutes after (B), five minutes after during peak effect (C) and twenty minutes after injection of 100 mg. per kg. of procaine amide (D).

of the peak contractile force to less than 40 per cent of its control was found to be incompatible with recovery and such animals died in acute cardiovascular collapse.

Mean blood pressure, heart rate and electrocardiographic intervals were also recorded during quinidine infusions. The results from three dogs given sublethal infusions of quinidine are summarized in Table I.

From the aforementioned experiments it became apparent that doses of quinidine (base) from about 20 to 30 mg. per kg. would produce submaximal negative inotropic effects. This was tested using single doses of quinidine gluconate and the results are included in Table II. In each case the effect of a given dose was evaluated in terms of the control tension. Time relations of the changes in contractility, blood pressure, heart rate and electrocardiographic intervals following these doses of quinidine are shown in Figure 2.

Procaine Amide: This compound was tested in four doses ranging from 10 to 100 mg. per kg. Definite negative inotropic effects were observed as shown in Figure 3. Results from

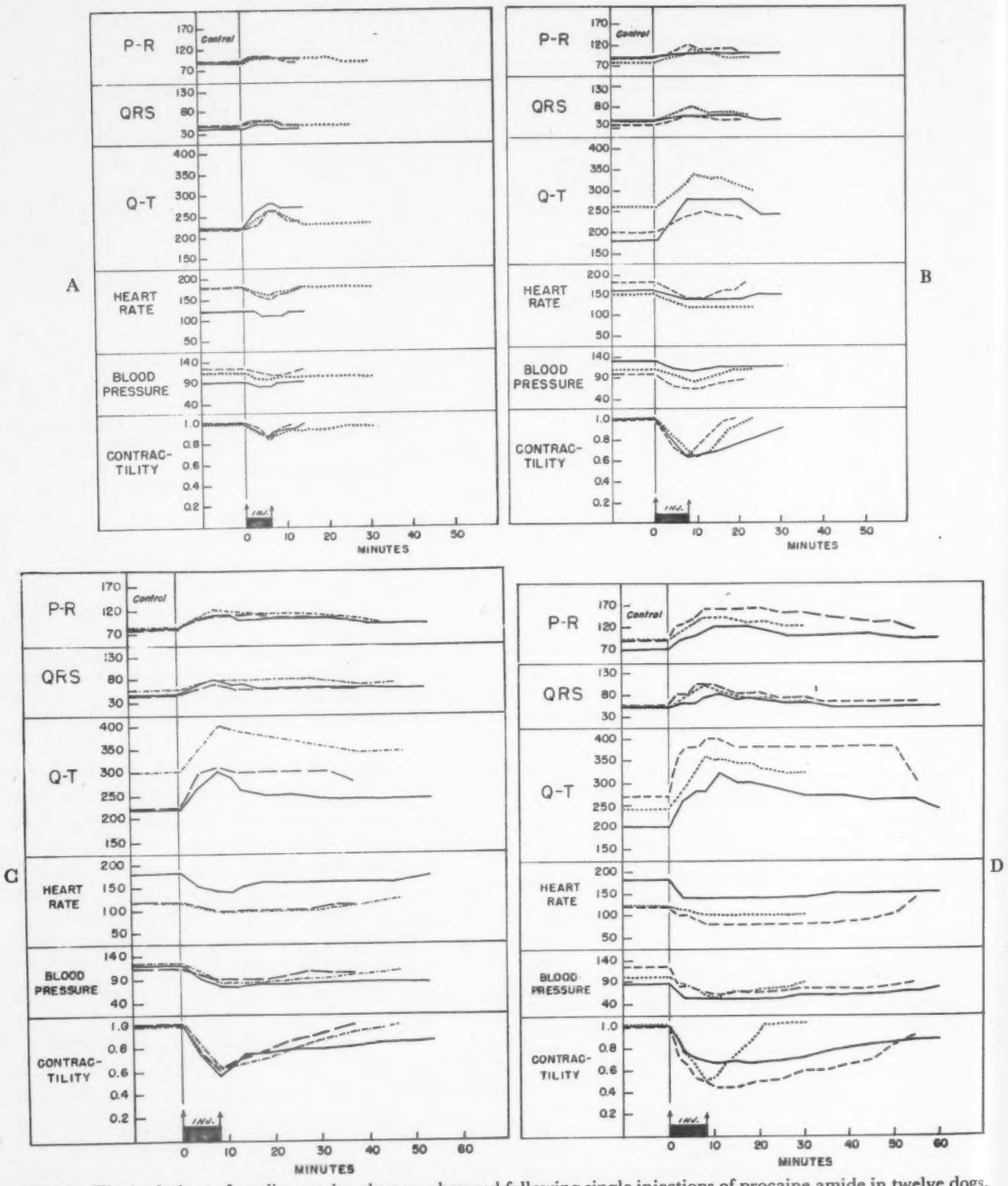

FIG. 4. Time relations of cardiovascular changes observed following single injections of procaine amide in twelve dogs. A, 10 mg. per kg. B, 25 mg. per kg. C, 50 mg. per kg. D, 100 mg. per kg.

twelve dogs are included in Table II. The time course of the changes observed are shown in Figure 4.

Quinidine vs. Procaine Amide: Dose response relations for the two drugs are shown in Figure 5. It is apparent that the negative inotropic effects of the two compounds are similar and can be described by a single regression. However, submaximal doses of procaine amide produce a less prolonged effect than similar

TABLE II
Inotropic Effects of Quinidine and Procaine Amide

Drug	Dose (mg./kg.)	Dog No.	Contractile Force (gm.)			Mean ± S.D. (Maximum Effect/Control)
			Control	Maximum Effect	Maximum Effect/ Control	
Quinidine base*	31	1	40	17	0.42	0.565 ± 0.117
		2	39	21	0.54	
		3	33	20	0.60	
		4	50	35	0.70	
	19	5	25	16	0.64	0.780 ± 0.107
		6	50	39	0.78	
		7	31	25	0.80	
		8	20	18	0.90	
Procaine amide hydrochloride	100	9	39	17	0.44	0.535 ± 0.112
		10	37	19	0.51	
		11	56	37	0.63	
	50	12	29	18	0.56	0.596 ± 0.035
		13	40	24	0.60	
		14	52	33	0.63	
	25	15	29	18	0.62	0.623 ± 0.005
		16	58	36	0.62	
		17	46	29	0.63	
	10	18	38	32	0.84	0.866 ± 0.023
		19	40	35	0.88	
		20	41	36	0.88	

* Injected as the gluconate.

doses of quinidine (Figs. 2 and 4). Considering the range of reversible effects only (i.e., 100 per cent to 40 per cent contractility), the median effective dose (that producing 50 per cent of maximal reversible response) would correspond to a depression of contractility to 70 per cent of control values. This is produced by about 25 mg. per kg. of procaine amide hydrochloride or the same amount of quinidine base (Fig. 5).

Character of the Negative Inotropic Changes: Myocardial tension curves (Figs. 1 and 3) are composed of three more or less distinct portions. There is first an early rapid phase of increasing tension lasting for approximately 0.06 second during which 80 to 100 per cent of the peak tension is developed. This is followed by a slow middle phase of increasing or decreasing tension lasting for about 0.10 second and a rapid terminal phase of decreasing tension of about 0.18 second. These probably correspond to isometric contraction, ejection and relaxation

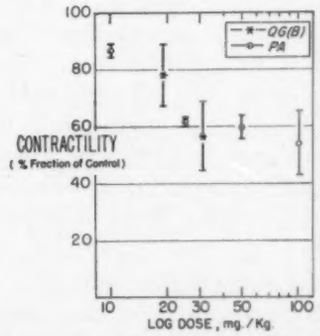

FIG. 5. Dose response relations of myocardial contractility following single doses of quinidine expressed as the base (QGB) and procaine amide (PA).

of the ventricle. From the tension curves obtained following quinidine (Fig. 1) it is apparent that the duration of the entire tension curve is increased to as much as 200 per cent of its control value. Similar results were obtained in all animals treated with quinidine. Some increase was noted in all phases, but the major fraction was associated with an increased duration of the middle slow phase. As a consequence of the increased duration and decreased peak tension, the rate of change of tension was markedly reduced following treatment. In the example shown in Figure 1 the first phase is reduced from a rate of 383 gm. per second to 150 gm. per second; and in the second phase from 40 gm. per second to 20 gm. per second.

In contrast to quinidine, administration of procaine amide produced minimal or no changes in the duration of the tension curve even when the peak tension was markedly reduced (Fig. 3).

Measurements of the area under the tension curve show a reduction of the time-tension values per beat following treatment with either antiarrhythmic agent. In the example for quinidine (Fig. 1), the area is reduced from 4.8 gram-seconds to 3.6 gram-seconds. Similarly for procaine amide (Fig. 3) the area is reduced from 4.6 gram-seconds of the control to 3.9 gram-seconds during peak depression of contractility.

Comments

From the data presented, it seems clear that both quinidine and procaine amide are capable of producing severe depression of myocardial contractility. These results are in agreement with previous statements about quinidine,[3] but contrast sharply with the presently accepted idea that procaine amide has little or no effect on contractility.[2,5] Nevertheless, they are in agreement with the conclusions reached by McClendon et al.[10] regarding the effect of procaine amide on the human heart. It is of interest that on a weight basis, the degree of depression is essentially the same for both drugs (Fig. 5). In man the therapeutic dose levels of these drugs are such that on a weight basis procaine amide hydrochloride is often used in amounts three to four times that of quinidine base.[2,5] Thus, it may take about three to four times the therapeutic dose of quinidine to produce the same degree of depression of contractility as the therapeutic dose of procaine amide. Furthermore, in the dog, antiarrhythmic doses of quinidine (5 to 10 mg. per kg. of the base) produce no detectable changes in contractility while antiarrhythmic doses of procaine amide (25 to 50 mg. per kg. of the hydrochloride) have definite negative inotropic effects.

Hypotension and Bradycardia: The effect of the two drugs on the electrocardiogram, heart rate and blood pressure are similar. The P-R, QRS and Q-T intervals are all prolonged. Calculation of the $Q\text{-}T_c$ interval showed that the increase in the Q-T interval was greater than can be accounted for by changes in heart rate. Administration of both drugs produced bradycardia and hypotension but the latter was more marked after administration of quinidine. Figures 2 and 4 show that the decrease in blood pressure parallels the decrease in contractile force. However, it is noteworthy that in all cases the changes in contractility were leading and those of blood pressure were lagging, as both decrease, reach a minimum point and then return toward normal. In general the contractile force returns to control values before the blood pressure does. These facts argue strongly against the possibility that hypotensive ischemic effects on the myocardium are responsible for the depression of contractility. On the other hand, part of the hypotensive effect of these drugs is undoubtedly due to reduction of contractile force which is superimposed upon the changes in peripheral resistance reported by others.[2,11,16]

Similarly, changes in heart rate could not account entirely for the observed inotropic effects as is readily apparent from the time course of the observed changes and by comparison of the effects produced by administration of quinidine and procaine amide. Further, other studies have shown that only minimal alterations in myocardial tension occur following changes in the heart rate alone.[14]

In general, the changes in the tension curves are undoubtedly complicated by the concurrent decrease in heart rate and blood pressure. However, these factors cannot account for the observed changes in the rate of developing tension.

Myocardial Potassium: Athough the basic mechanism of action of these drugs is not known, it appears likely that their negative inotropic effects may be related to changes in the ionic balance across the myocardial fibers. Sympathomimetic pressor agents and digitalis increase contractile force and produce a simultaneous net loss of myocardial potassium.[17–20]

Drugs which depress contractility, such as anesthetic agents[21] and nitroglycerin,[22] produce a simultaneous net gain of potassium by the myocardial cells. Quinidine[3,17,23,24] and perhaps procaine amide affect the myocardial balance of potassium in a similar manner, producing a net increase in cellular potassium. Thus, the negative inotropic effect of these compounds may be atrributable to a gain in intracellular potassium. Further, lowering the extracellular concentration of potassium has been reported to block the negative inotropic effect of quinidine on the isolated rabbit's atria.[3] At present it is not entirely clear whether the antiarrhythmic effect is also dependent upon this action on intracellular potassium. However, it is noteworthy that under certain experimental conditions a net loss of intracellular potassium is often associated with arrhythmias.[22] In addition, it is of interest that certain experimental antiarrhythmic agents were also found to possess negative inotropic properties.[26] Nevertheless, as pointed out elsewhere,[27] quinidine and procaine amide have been shown to exhibit distinct differences regarding their antiarrhythmic properties.

Molar Sodium Lactate: Recent work with quinidine[28,29] and procaine amide[25] indicates that their toxicity may be related to a metabolic acidosis produced by these agents. Although it is not known whether the primary mechanism involved is an alteration of electrolyte balance with subsequent changes in pH or vice versa, the significant observation was made that molar sodium lactate may be useful in treating clinically observed toxicities to quinidine and procaine.[25,28,29] Administration of molar sodium lactate reverses the electrocardiographic signs of toxicity and restores blood pressure to normotensive levels as it corrects the metabolic acidosis. It would be of interest to determine whether sodium lactate would also prevent or reverse the negative inotropic effects of these drugs.

Summary

Quinidine and procaine amide were tested in experiments on dogs regarding their ability to alter myocardial contractility. Myocardial tension was measured directly by a strain gauge arch attached to the left ventricle *in vivo*. Both drugs in doses greater than 20 mg. per kg. depress contractility and their effects are similar on a weight basis. Considering that the therapeutic doses of procaine amide are generally larger than those of quinidine, the negative inotropic effect of the former is therapeutically more significant than that of the latter. The drugs altered the contractile tension curves in a characteristic manner so that both the peak contractile tension and the area under the tension-time curve were reduced. Reduction of the peak contractile tension to less than 40 per cent of its control value was found to be incompatible with subsequent recovery. Changes of a lesser magnitude were generally reversible.

Administration of both drugs produced bradycardia and hypotension. The decrease in blood pressure followed the change of contractility. Both returned to control values during recovery. It is suggested that the negative inotropic effects of these drugs may be related to their known ability to increase the intracellular concentration of potassium in the myocardium.

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Experimental Bilateral Bundle Branch Block*

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THE major purpose of this paper is to amplify and substantiate the interpretation of previously published experimental data[1] demonstrating that electrocardiographically complete bundle branch block and complete atrioventricular block result in minimal mechanical asynchronism in onset of ventricular contraction. This is based on the assumption that surgical section of either bundle branch resulted in complete, not incomplete, bundle branch block. The experimental results validating this assumption are herein illustrated. The electrocardiographic pattern of complete bundle branch block is, *per se*, not sufficient evidence that complete rather than incomplete bundle branch block has been produced.

We also wish to re-emphasize the concept of bilateral bundle branch block and to demonstrate that such lesions may be readily produced in dogs. In a recent review of the literature, Rosenbaum and Lepeschkin[2] found only nine cases of bilateral bundle branch block in which the diagnosis was acceptable. These investigators emphasized that many cases of complete atrioventricular block are probably due to bilateral bundle branch block rather than to organic or functional lesions of the atrioventricular node or bundle of His. Unfortunately, differentiation between these causes of complete atrioventricular block is not possible during life; even detailed postmortem studies may fail to resolve these difficulties. The accepted cases of bilateral bundle branch block were characterized by alternating or intermittent patterns of right and left bundle branch block in the same patient, accompanied by changes in the P-R interval.

METHODS AND MATERIAL

Right and left ventricular pressure curves were registered simultaneously in thirty-two dogs under anesthesia (with 30 mg./kg. of pentobarbital sodium administered intravenously) with the chest open, during sinus rhythm. The electrocardiogram was recorded simultaneously, generally using lead V_5. Respiration was maintained by intermittent inspiratory positive pressure.

Plastic catheters, 1.5 mm. internal diameter, were sewn into the right and left ventricular chambers† and connected to Statham P23AA strain gauges with 48 inch lengths of black polyvinyl tubing.‡ Pressures were recorded on a photographic 6-channel unit.§ After suitable control observations, right or left bundle branch block was produced by local mechanical injury to the upper portion of the ventricular septum on the right or left side. Typical electrocardiographic changes of right or left bundle branch block were noted in lead V_5. In some dogs, the bundle branch block spontaneously reverted to the control electrocardiographic pattern after one or two hours, permitting subsequent production of the contralateral type of bundle branch block. In other dogs the initially produced bundle branch block persisted. In some of the latter studies, bilateral bundle branch block was subsequently produced, resulting in an electrocardiographic pattern of complete heart block with an idioventricular rhythm.

Simultaneous right and left ventricular curves were recorded with lead V_5 in thirty-two dogs during sinus tachycardia with normal QRS complexes, in twenty-five dogs with right bundle branch block, in thirteen dogs with left bundle branch block, in twelve dogs with complete heart block and a left idioventricular focus, and in eleven dogs with complete heart block and a right idioventricular focus. During complete heart block, a widened aberrant QRS complex, upright in lead V_5, resulted from a right ventricular idioventricular focus. A left ventricular focus produced a widened QRS complex

† Identical systems were employed for the right and left ventricles.

‡ U. S. Catheter Company, Glens Falls, New York.

§ Electronics for Medicine, White Plains, New York.

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This work was supported in part by a grant from the Florida Heart Association and from the National Heart Institute, H-2735.

TABLE 1

Relationship Between Onset of Isometric Contraction of the Right and Left Ventricles (in seconds)*

Dog No.	Sinus Tachycardia Normal QRS		Sinus Tachycardia Right Bundle Branch Block		Sinus Tachycardia Left Bundle Branch Block		Complete A-V Block Left Ventricular Focus		Complete A-V Block Right Ventricular Focus	
	Range	Mode	Range	Mode	Range	Mode	Range	Mode	Range	Mode
4	−0.02 to +0.01	−0.01	−0.01 to +0.01	0.00	...	...	...	...	...	...
5	+0.02 to +0.03	+0.03	+0.01 to +0.03	+0.02	...	...	...	...	...	...
7	−0.02 to +0.01	−0.01	+0.04 to +0.04	+0.04	...	...	...	...	...	...
13	0.00 to +0.02	0.00	0.00 to +0.04	+0.02	...	...	...	...	...	...
14	0.00 to +0.02	+0.02	+0.01 to +0.01	+0.01	...	...	...	...	...	...
15	−0.01 to 0.00	0.00	0.00 to +0.01	0.00	...	...	...	...	...	...
17	+0.01 to +0.01	+0.01	−0.01 to +0.01	+0.01	...	...	...	...	...	...
19	0.00 to 0.00	0.00	0.00 to +0.02	+0.02	...	...	...	...	...	...
21	−0.02 to −0.01	−0.02	+0.01 to +0.02	+0.02	...	...	...	...	...	...
24	0.00 to 0.00	0.00	+0.02 to +0.02	+0.02	...	...	...	...	...	...
25	0.00 to 0.00	0.00	+0.01 to +0.02	+0.01	...	...	...	...	...	...
26	0.00 to +0.01	0.00	+0.02 to +0.03	+0.02	...	...	...	...	...	...
28	0.00 to 0.00	0.00	0.00 to +0.04	+0.02	...	...	...	...	...	...
31	0.00 to +0.01	0.00	+0.02 to +0.02	+0.02	...	...	...	...	...	...
33	−0.01 to 0.00	−0.01	...	...	−0.04 to −0.02	−0.04	+0.00 to +0.03	+0.02	...	...
34	+0.02 to +0.02	+0.02	+0.01 to +0.01	+0.01	−0.01 to 0.00	0.00	+0.01 to +0.02	+0.01	−0.01 to 0.00	−0.01
35	−0.01 to +0.01	0.00	...	...	...	...	0.00 to +0.01	0.00	−0.03 to −0.01	−0.02
36	−0.02 to −0.01	−0.01	+0.01 to +0.02	+0.01	...	...	...	...	...	...
37	−0.02 to 0.00	0.00	0.00 to +0.02	+0.01	−0.02 to −0.02	−0.02	−0.01 to +0.02	+0.01	−0.02 to −0.00	0.00
38	+0.01 to +0.01	+0.01	0.00 to +0.01	0.00	−0.01 to −0.02	−0.02	...	...	−0.04 to −0.05	−0.04
39	−0.01 to −0.01	−0.01	+0.02 to +0.03	+0.02	−0.03 to −0.04	−0.03	...	...	...	...
40	−0.02 to −0.01	−0.01	+0.02 to +0.04	+0.02	...	...	+0.02 to +0.02	+0.02	−0.01 to +0.01	0.00
41	−0.01 to −0.01	−0.01	0.00 to 0.00	0.00	−0.02 to −0.02	−0.02	+0.01 to +0.02	+0.02	−0.02 to −0.01	−0.02
42	−0.02 to −0.01	−0.02	...	...	−0.03 to −0.04	−0.03	0.00 to 0.00	0.00	−0.02 to −0.04	−0.03
43	+0.01 to +0.01	+0.01	+0.01 to +0.02	+0.02	...	...	+0.01 to +0.02	+0.01	−0.01 to −0.01	−0.01
44	−0.01 to 0.00	0.00	...	...	−0.02 to −0.02	−0.02	0.00 to +0.02	+0.02	...	...
45	+0.01 to +0.01	+0.01	...	...	0.00 to 0.00	0.00	+0.02 to +0.02	+0.02	−0.01 to 0.00	−0.01
46	−0.01 to −0.01	−0.01	...	...	0.00 to 0.00	0.00	−0.01 to +0.02	+0.02	−0.02 to 0.00	−0.02
47	+0.02 to +0.02	+0.02	+0.01 to +0.02	+0.01	...	...	...	...	...	...
48	−0.02 to −0.01	−0.01	0.00 to −0.00	0.00	−0.03 to −0.02	−0.02	0.00 to +0.02	0.00	...	...
49	0.00 to +0.01	+0.01	0.00 to +0.01	0.00	−0.02 to −0.01	−0.02	...	...	...	...
50	+0.02 to +0.02	+0.02	...	...	+0.02 to +0.02	+0.02	...	...	−0.02 to 0.00	0.00
Av.	...	0.00	...	+0.01	...	−0.02	...	+0.01	...	−0.01

* Negative values signify earlier onset of right ventricular contraction. Positive values signify earlier onset of left ventricular contraction.

predominantly downward in lead V_5. The justification for these interpretations has been discussed elsewhere.[3]

The difference in electrical-mechanical transmission time in this recording system was 0.004 second as determined by the method of Gordon et al.[4] This interval was not considered significant, since the electrical-mechanical time intervals are reported only to the nearest 0.01 second interval in the present study.

RESULTS

The data obtained in this study are outlined in Table 1. During sinus rhythm the mode relationship for the onset of isometric contraction in the two ventricles was 0.00 second, signifying simultaneous onset of ventricular contraction. The range is −0.02 to +0.03 second. That is, at one extreme, right ventricular contraction began 0.02 second prior to the left; at the other extreme, left ventricular contraction was initiated 0.03 second earlier than the right. In most instances the onsets of ventricular contraction were either temporally identical or one ventricle contracted 0.01 second prior to the other. Negative values in Table 1 arbitrarily signify earlier onset of right ventricular contraction. Positive values signify earlier onset of left ventricular contraction.

The relationships between the onset of ventricular contraction during right and left bundle branch block and complete heart block with idioventricular rhythm are shown in Table 1. The control mode value for relative onset of right and left ventricular contraction is 0.00 second; in twenty-five dogs with right bundle branch block, the onset of right ventricular isometric contraction was 0.01 second later than the left. In thirteen dogs with left bundle branch block, left ventricular contraction began 0.02 second after the right. In twelve dogs with idioventricular rhythm, this relationship was +0.01 second (left ventricular contraction preceding the right) during beats originating in the

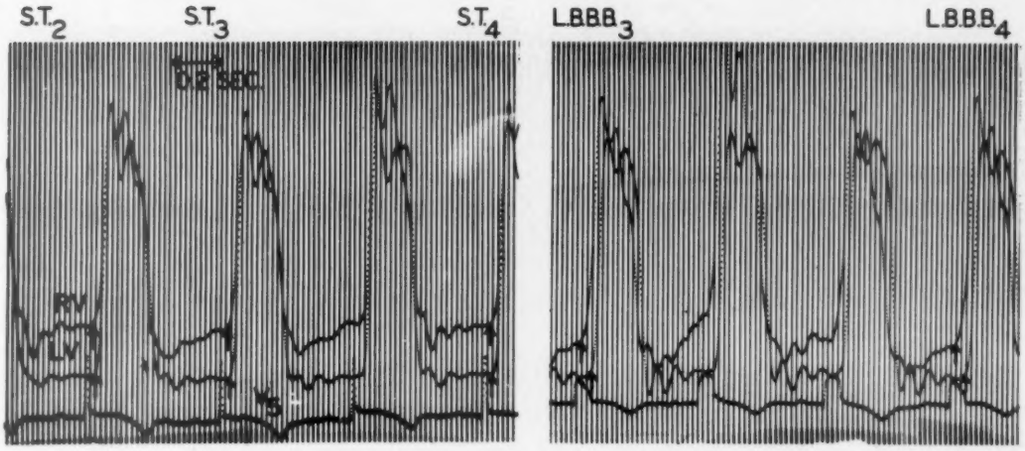

FIG. 1. Dog 33. The control electrocardiogram (lead V_5) is shown on the left; left bundle branch block is present on the right. Right and left ventricular pressure curves are presented.

left ventricle; in eleven dogs with idioventricular beats starting in the right ventricle, contraction of the latter ventricle began 0.01 second prior to that of the left.

On statistical analysis, data are available for twenty-five dogs in both sinus tachycardia and right bundle branch block (columns 1 and 2, Table 1). The mode values during sinus rhythm and right bundle branch block are 0.00 and +0.01 second, respectively. This difference is statistically significant ($0.01>P>0.001$). Thirteen dogs are represented in both columns 1 and 3. The mode values are 0.00 and −0.02 second ($P<0.001$). Comparison of the values of twelve dogs in both sinus rhythm and complete heart block with a left ventricular idioventricular focus (columns 1 and 4, Table 1) reveals mode data of 0.00 and +0.01 second, respectively ($0.01>P>0.001$). In a similar fashion, the difference in mode value between columns 1 and 5, sinus rhythm and right ventricular idioventricular rhythm, is statistically significant for eleven dogs ($0.01>P>0.001$).

Studies are available on seven dogs with both right and left bundle branch block. The mode values for relative onset of right and left ventricular isometric contraction are +0.01 and −0.02 second, respectively ($0.01>P>0.001$). Similarly, data are present for nine dogs in complete heart block with right and left idioventricular beats. The mode values for onset of ventricular contraction are −0.01 and +0.01 second, respectively ($P<0.001$).

The relationship between onset of ventricular contraction during right bundle branch block and complete heart block with a left ventricular idioventricular focus (in six dogs) was similar; the mode values are +0.01 and +0.01 second, respectively ($0.7>P>0.6$). There is no difference in the relative onset of ventricular contraction during left bundle branch block and complete heart block with a right ventricular idioventricular focus; the mode values are −0.01 and −0.02 second, respectively ($0.2>P>0.1$).

Some of these relationships are illustrated in Figures 1 through 6. In Figure 1, right and left ventricular pressure curves are recorded simultaneously with lead V_5 before and after production of left bundle branch block. Under control conditions, right ventricular contraction starts 0.01 second before the left. During left bundle branch block, left ventricular contraction started 0.04 second after the right. However, during complete heart block with a left ventricular idioventricular focus (Figs. 2 and 3), left ventricular contraction started 0.02 second prior to the right. Section of the right bundle branch after the left resulted in complete heart block with an idioventricular rhythm.

In Figure 4, the control onset of isometric contraction is temporally identical in the two ventricles. Section of both bundle branches (Figs. 5 and 6) again produced complete heart block with an idioventricular rhythm. During a left ventricular focus, left ventricular contraction was initiated 0.01 second prior to the right. During a right ventricular focus, the onsets were identical in time.

In summary, the normal range for the relative onset of right and left ventricular isometric contraction is from 0.02 second, right ventricle ahead, to 0.03 second, left ventricle ahead (Table 1). In twenty-four of twenty-five dogs

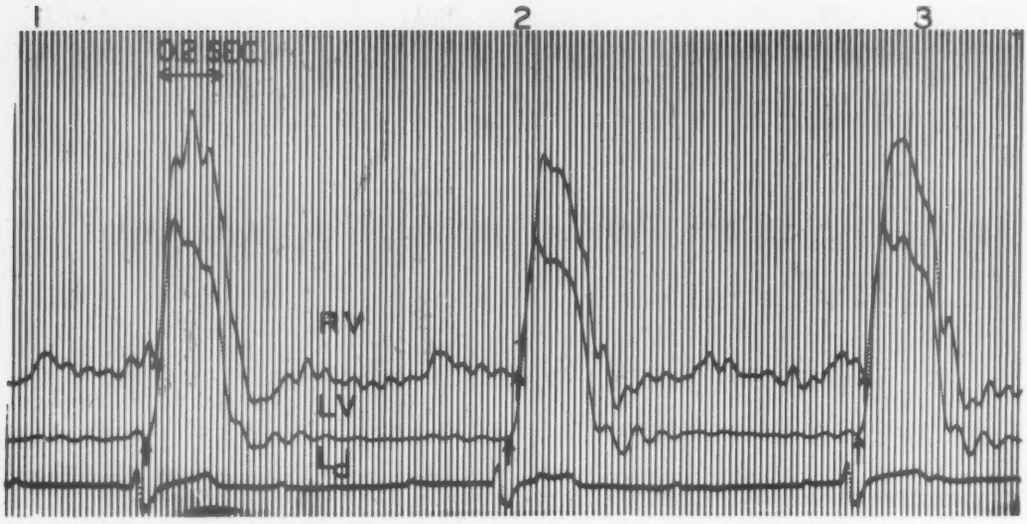

FIG. 2. Dog 33. Complete atrioventricular block has developed after section of the left and right bundle branches in that order.

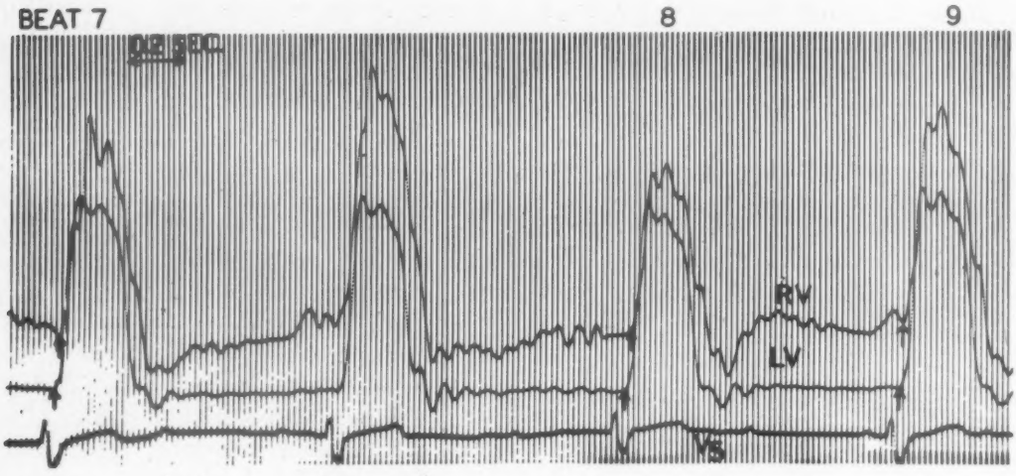

FIG. 3. Dog 33. Further evidence of complete heart block.

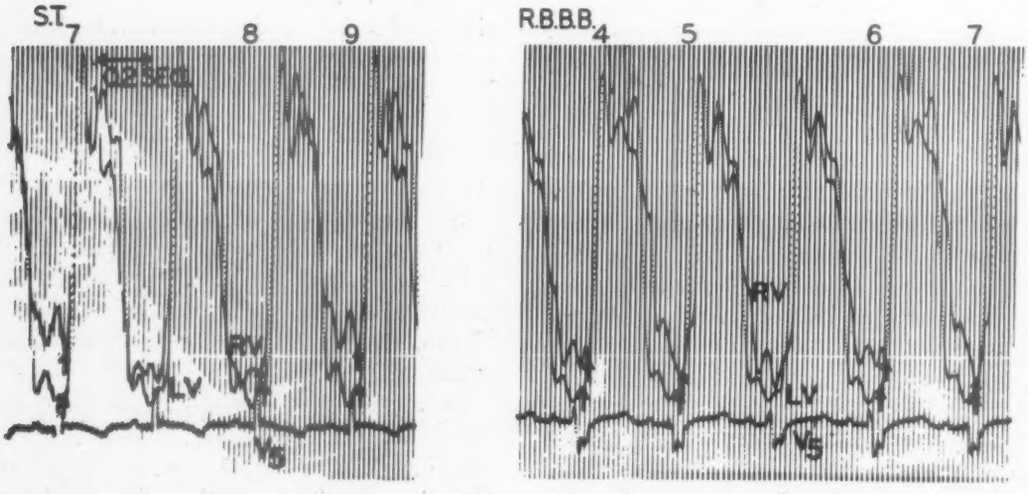

FIG. 4. Dog 37. Sinus rhythm is present prior and subsequent to the production of right bundle branch block.

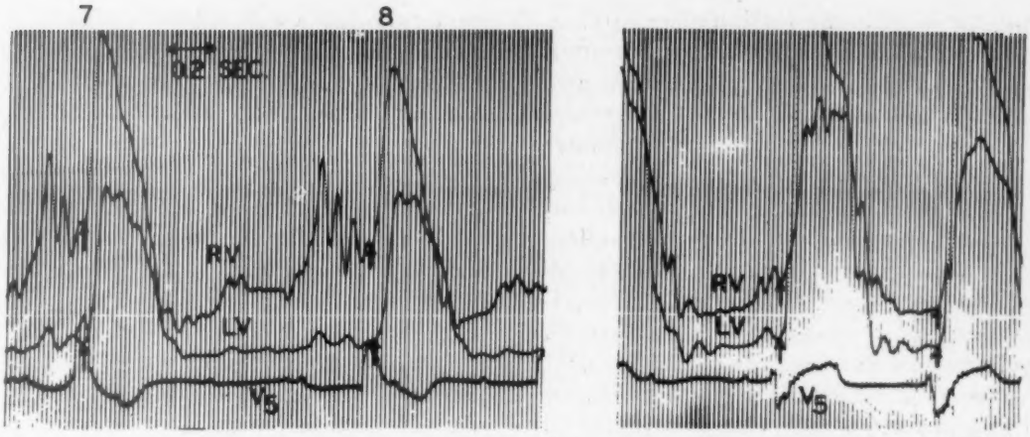

FIG. 5. Dog 37. Complete atrioventricular block is present after section of first the right and then the left bundle branch. *Left*, right ventricular focus. *Right*, left ventricular focus.

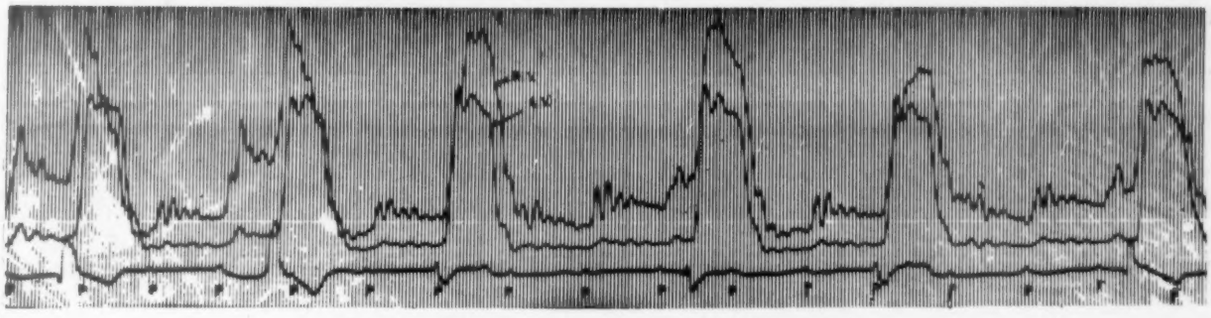

Fig. 6. Dog 37. Complete heart block is noted.

with right bundle branch block, in ten of thirteen dogs with left bundle branch block, in all twelve dogs with complete heart block and a left ventricular idioventricular focus, and in nine of the eleven dogs with complete heart block and a right ventricular idioventricular focus, the relative onsets of ventricular isometric contraction continue to fall within normal limits.

The data also demonstrate that complete heart block with an idioventricular focus results from section of both the right and left bundle branches. In eight dogs (Table 1) the initially produced left bundle branch block was followed by complete heart block after section of the right bundle. In six dogs the initially produced right bundle branch block was followed by complete heart block after section of the left bundle. As noted herein, in some dogs surgically produced bundle branch block spontaneously disappeared so that observations during right and left bundle branch block and also complete heart block could be made. In no instance was complete heart block produced during attempts to produce right or left bundle branch block. In dog 35, pressure curves were not obtained during the initially produced right bundle branch block.

COMMENTS

The degree of mechanical asynchronism resulting from right and left bundle branch block and complete heart block was noted to be 20 to 30 milliseconds (instead of the theoretically expected 80 milliseconds)* in the studies previously outlined.[1] The question of whether this limited degree of mechanical asynchronism re-

* It has been demonstrated in experimental bundle branch block in the dog that the free wall of the ipsilateral ventricle on the interrupted side is depolarized about 0.04 second after the contralateral normally depolarized ventricle. This interval is the period required for transseptal electrical depolarization.[5,6] In right and left bundle branch block, electrical depolarization differences of at least 0.08 second would therefore be anticipated. This time interval is the algebraic difference between the expected differences in the onset of ventricular electrical depolarization in right bundle branch block (+0.04 second, left ventricle ahead) and in left bundle branch block (−0.04 second, right ventricle ahead). If electrical asynchronism resulted in mechanical asynchronism it would thus be expected that the onset of right ventricular isometric contraction would precede that of the left ventricle by 0.04 second in left bundle branch block; the reverse order of onset of isometric contraction would be anticipated in right bundle branch block. The over-all mode difference would be 0.04 (−0.04 second), or 0.08 second.

sulted from the surgical production of incomplete right or left bundle branch block, or from a basic lack of correlation between electrical and mechanical asynchronism in the cardiac cycle, required consideration. Because of the anatomy of the two bundle branches, there was difficulty in ascertaining that the surgical approach had resulted in complete rather than incomplete bundle branch block. The right bundle is a discrete structure for much of its length. Experimental production of right bundle branch block is relatively easy in the dog. In man, transient right bundle branch block is a common occurrence during passage of a Cournand catheter tip through the right ventricle in the course of right heart catheterization. Transient left bundle branch block has not been observed in this laboratory in the course of more than 120 left heart catheterizations with the tip of a polyethylene catheter lying free in the cavity of the left ventricle. The left bundle branch both in man and the dog[7] spreads out fanwise on the left surface of the ventricular septum a short distance distal to the onset of the left bundle from the bifurcation of the bundle of His. Complete surgical section of the left bundle is, therefore, more difficult than interruption of the right bundle.

Proof of surgical production of complete as opposed to incomplete bundle branch block may be obtained on histological or on functional grounds as discussed by Wilson and Herrmann.[8] These investigators state that "a functional test is just as conclusive as histological examination." The functional test referred to by Wilson and Herrmann is as follows: Complete bundle branch block is produced initially; the other bundle branch is then cut. "If complete heart block resulted, and if, on microscopic examination, the second cut was so placed as to make injury to the main stem of the bundle improbable, we regarded the proof that we were in the first instance dealing with unilateral block as complete."[8]

It is conceivable that in the six dogs in the present study in which right bundle branch block was produced initially, followed by complete heart block after section of the left bundle, that the main bundle of His rather than the left bundle was severed by the latter procedure. However, the same technic for left bundle branch section was followed in eight other dogs. In these latter eight animals, section of the left bundle produced left bundle branch block with sinus rhythm and a widened QRS complex rather than the complete atrioventricular block with a QRS complex of normal duration which would have resulted had the bundle of His itself been sectioned. Subsequent section of the right bundle branch resulted in complete heart block with an idioventricular rhythm. Since the right bundle is a discrete structure and easily sectioned, the results in these eight dogs indicate that first the left and then the right bundle was completely sectioned and suggest strongly that the surgical procedure for left bundle branch section (for all fourteen dogs in this study) resulted in disruption of the left bundle itself and not the bundle of His. The fact that bilateral bundle branch section produced complete heart block with a slow idioventricular rhythm in fourteen dogs is in turn a demonstration that the surgical technic employed produced complete bundle branch block. Thus the small differences in the relative onsets of right and left ventricular isometric contraction after production of bundle branch block may be attributed to limited correlation of mechanical and electrical events in the cardiac cycle. Studies in man[9,10] on electrical-mechanical relationships have not conclusively proved the existence of physiologically significant asynchronism in the onset of ventricular contraction in patients with bundle branch block.

Other investigators[8,11] have also produced complete heart block by section of both bundle branches. These studies, and a review of the literature on bilateral bundle branch block in man, suggest that some cases of complete heart block in man are due to bilateral bundle branch disease. Anatomic studies of the bundle branches by Yater[12,13] have demonstrated that both bundle branches are commonly diseased in human cases of bundle branch block, thus establishing an anatomic substrate for complete heart block secondary to bilateral bundle branch block. Positive clinical recognition of these cases awaits future study.

Summary

Surgical production of bilateral bundle branch block resulted in complete heart block in fourteen dogs. In eight dogs, left bundle branch block resulted from the initial bundle branch section. In six animals, right bundle branch block was produced at first. In either circumstance, section of the opposite bundle branch resulted in complete heart block. Limited correlation between the electrical and

mechanical events of the cardiac cycle under these circumstances was demonstrated.

The data indicate that complete right and complete left bundle branch block were produced by surgical section of the respective bundle branches.

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Reports on Therapy

Preliminary Evaluation of Ro 2-5803—An Antiarrhythmic Agent*

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THE SEARCH for effective agents for the control and reversal of cardiac arrhythmias is not obviated by the establishment of the effectiveness of digitalis, quinidine, procaine amide and other drugs in their proper applications. It would be desirable to obtain a drug with relatively low toxicity especially when a relative clinical refractoriness demands "pushed" dosages as well as a drug which presented limiting clinical or electrocardiographic factors different from those possessed by quinidine and procaine amide.

A potential antiarrhythmic drug, 2,6-bis (1 - piperidylmethyl) - 4 - (α,α - dimethylbenzyl) phenol dihydrobromide (Ro 2-5803), has been evaluated in mice, rats and dogs, as well as in the isolated auricle of the rabbit.[1] In mice it has been found somewhat more toxic than quinidine sulfate, given intravenously, intraperitoneally and orally, as well as in rats given the drug orally. The intravenous and oral median lethal dose in mice was found to be 30 to 330 mg./kg., respectively, compared with values of 54 and 535 mg./kg. for quinidine; the oral median lethal dose for rats was 600 mg./kg. of Ro 2-5803, compared with 967 mg./kg. for quinidine. Oral doses of 10 mg./kg. were tolerated by two dogs for a ten-day period, but two others receiving 50 mg./kg. for three days began to vomit on the fourth day. The median effective dose of Ro 2-5803 and quinidine in dogs with acetylcholine-induced atrial fibrillation was virtually the same: the ED_{30} in the isolated auricle of the rabbit (Dawes method) for Ro 2-5803 was about one-third of that for quinidine.

We tested Ro 2-5803 in a group of human subjects with and without heart disease, with sinus rhythm, atrial fibrillation and atrial flutter. Some patients with one of the latter two conditions also exhibited abnormal ventricular irritability and/or conduction.

MATERIAL AND METHODS

RO 2-5803 was administered intravenously forty-five times to twenty-nine patients in dosages from 1 mg. to 200 mg.

Tolerance Testing: A total of twenty-two tests were first conducted on fourteen subjects with and without organic heart disease to test the effect of intravenously administered doses of Ro 2-5803, beginning with 1 mg. total dose (about 0.01 mg./kg.) and increasing gradually to total doses of 100 mg. (1.2 to 1.9 mg./kg.). Patients were carefully observed for changes in pulse, blood pressure, respiratory function, general clinical reaction and in the electrocardiogram. In these preliminary tests no essential clinical cardiovascular or electrocardiographic alterations occurred; no side effects were observed. This series of tests determined the tolerance to the drug and more extensive studies were then undertaken, generally employing 100 mg. doses.

Group I. Patients with Normal Sinus Rhythm: A total of fourteen tests were carried out on twelve patients with basic sinus rhythm.

Group IA. Patients with Normal Cardiovascular Systems: Of the twelve patients, there were five (three women and two men), ranging in age from twenty-five to seventy-one years, with no known organic heart disease. These patients underwent seven test periods.

Group IB. Patients with Cardiovascular Disease: The remaining seven patients with normal sinus rhythm (four men and three women) ranged in age from forty-seven to sixty-two years. All had organic heart disease: two had hypertensive cardiovascular disease, one had arteriosclerotic heart disease, two

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had both hypertensive and arteriosclerotic heart disease, one had hypertensive vascular disease and one had rheumatic valvular heart disease. Previous medication consisted of administration of anticoagulants, digitalis, diuretics, reserpine and tertiary amines.

Except for one patient who was given 150 mg., the patients received 100 mg. of Ro 2-5803 intravenously per test. The drug was administered slowly by venipuncture following baseline electrocardiogram and blood pressure determinations. Blood pressure determinations, an electrocardiogram using a predetermined single lead and general clinical observations were made in serial fashion, for the most part at one, three, five, ten, fifteen and thirty minutes and at one and two hours.

The electrocardiograms were analyzed for rate, QRS duration and contour changes, P wave changes, P-R intervals, and Q-T and Q-T_c intervals. Arithmetic means of the entire group were determined for rate, systolic, diastolic and mean blood pressure, QRS duration, Q-T and Q-T_c values. Mean blood pressure was determined by adding one-third of the pulse pressure to the diastolic pressure. The other data did not lend themselves to determinations of a mean.

Group II. Patients with Atrial Fibrillation or Flutter: A total of nine tests were conducted on eight patients (four women and four men), ranging in age from forty-five to seventy-two years, with either atrial fibrillation or flutter as baseline mechanisms. Some of these patients exhibited abnormal ventricular irritability or conduction in addition to the supraventricular arrhythmia. All had received other medications: digitalis, reserpine and anticoagulants. Each test was carried out with a 100 mg. dose of Ro 2-5803 given intravenously following baseline determinations as described under Group I.

The data were analyzed for the same information; in these patients, however, averages of five or more complexes were employed to determine ventricular rates, R-R and Q-T intervals. When atrial rates were measurable, the duration of fifteen to thirty atrial cycles was determined and an arithmetic mean found.

Results

Group I. Patients with Normal Sinus Rhythm

Clinical Side Effects: There were no unusual symptoms except in one patient who had gallstones and colitis and who complained of burning sensations in the abdomen which lasted five minutes; this was accompanied by depression of the T wave.

Blood Pressure Changes: The average mean, systolic and diastolic pressures for the entire group during the study demonstrated no notable change or development of hypotension.

Electrocardiogram: Within the first three minutes after the injection, there was an increase of rate in eleven of fourteen tests. In all patients there was a prolongation of the Q-T_c interval, when related to the rate. Actually, in the patients with an increase of rate there was a shortening of the Q-T interval but not in proportion to the increase in rate.

There was no essential change in the P wave, P-R interval, QRS configuration or S-T takeoff.

There was a widening of the QRS complex in two of the fourteen tests: (1) from 0.10 to 0.12 second at thirty seconds which persisted for sixty minutes, when it returned to 0.10; and (2) from 0.06 to 0.08 second in one minute with a gradual return to 0.06 within fifteen minutes.

The contour of the T wave changed in two of the fourteen tests: (1) 3 mm. to 1 mm. in one minute with a gradual return to 3 mm. by ten minutes; and (2) -4 mm. to -1 mm. at one-half minute with a return to -3.5 mm. at thirty minutes.

Group IA. Patients with Normal Cardiovascular Systems: Of the five patients with normal cardiovascular systems, there were two whose QRS duration was increased by 0.02 second and one who lost positivity of the T wave. Four of five patients showed an increased Q-T_c interval by at least 0.02 second within one to three minutes. The blood pressure did not drop in any patient. The blood pressure of one patient increased from a baseline of 155/80 mm. Hg to a maximum of 185/100 mm. Hg three to five minutes after injection of 100 mg. of Ro 2-5803; this was associated with an increase in pulse rate of 23/minute (82 to 105) in the first minute, after which there was a rapid return of the pulse rate and gradual return of the blood pressure to resting levels.

Group IB. Patients with Cardiovascular Disease: Of the remaining seven patients with cardiovascular disease none had increased QRS duration and in three positivity of T waves was increased by 1 mm. Two patients had increased Q-T_c intervals by 0.10 and 0.04 second; three increased Q-T_c interval by 0.01 to 0.02; one showed no change and one a reduced Q-T interval duration by 0.015 second. No significant blood pressure changes occurred.

Group II. Patients with Arrhythmias

Because of the changes that occurred in the eight patients with atrial fibrillation or atrial

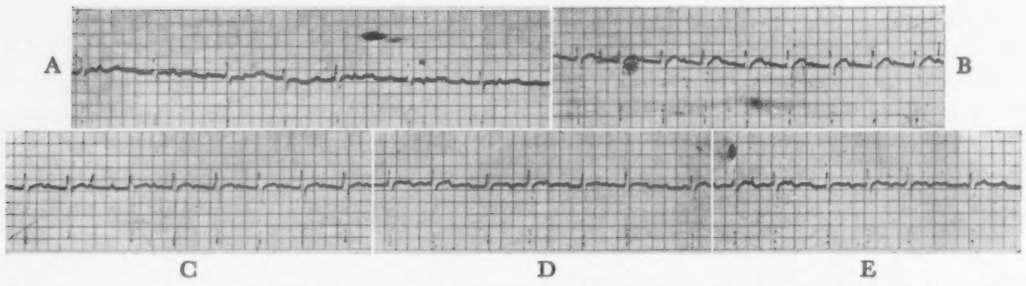

FIG. 1. Case 12. A sixty-five year old man with atrial flutter. Lead V_2. A, control. Slow flutter with a variable degree of A-V block. Auricular rate 195/minute. Ventricular rate approximately 60/minute. B, one minute after intravenous injection of 100 mg. Ro 2-5803. Normal sinus rhythm. Rate 82/minute. P-R interval 0.36 second. C, three minutes. Variable degree of A-V block. Auricular rate 170/minute. Ventricular rate approximately 80/minute. D and E, fifteen and thirty minutes. Return to control levels.

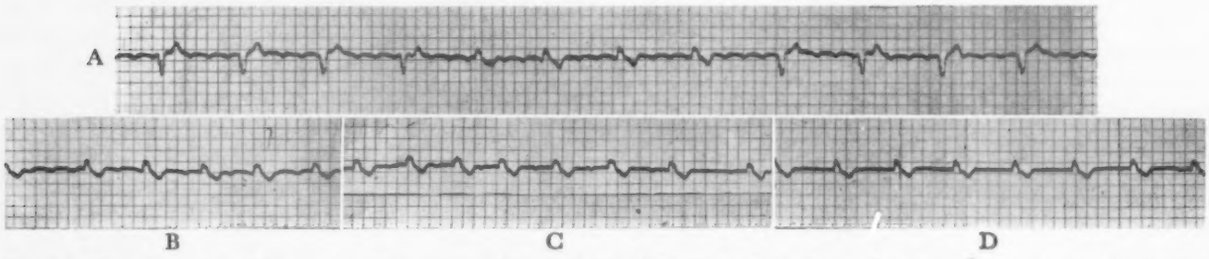

FIG. 2. Case 14. An eighty year old woman with probable digitalis intoxication. Lead III. A, control. Auricular flutter with auricular rate 180/minute. P waves inverted. Ventricular rhythm alternates between a 4:1 response with right bundle branch block and complete heart block. B, one minute after intravenous injection of 100 mg. Ro 2-5803. Auricular complexes of lower voltage and difficult to identify. Ventricular complexes show right bundle branch block. Complete heart block complexes have disappeared. C, five minutes. Sinus arrhythmia with first degree heart block (P-R interval = 0.32 second). Right bundle branch block persists. P waves of lower voltage than previous tracings. D, seven minutes through thirty minutes. Apparent supraventricular rhythm. Right bundle branch block. P waves not identified, except possibly in the last cycle.

flutter, individual descriptions of changes of rhythm in these patients follow:

CASE 6. Baseline mixture of atrial flutter with irregular degree of A-V block and atrial fibrillation, plus occasional ventricular premature beats or aberrant ventricular response. From three to fifteen minutes after drug administration maximal atrial slowing occurred (240 to 212).

CASES 7, 15, 22 and 25. Atrial fibrillation remained essentially unchanged. One patient (Case 15) had ventricular premature beats, unchanged by administration of the drug.

CASE 12. Slow atrial flutter with variable degrees of A-V block (Fig. 1). There was a 1:1 A-V response at one minute associated with an increase of ventricular rate (60 to 82/minute) and a slowing of the auricular rate (195 to 82/minute). The P-R interval was 0.36 second. At three minutes the auricular rate increased to 170/minute and a variable degree of A-V block returned. The ventricular rate was 80/minute. There was a gradual return to the control level by fifteen minutes.

CASE 14. Auricular flutter (180/minute) (Fig. 2). Ventricular rhythm alternated between a 4:1 response with right bundle branch block and complete heart block. At one minute the auricular complexes were of lower voltage and difficult to identify; complete heart block complexes were absent. At five minutes there was sinus arrhythmia with first degree heart block (P-R interval = 0.32 second). The auricular rate decreased; the ventricular rate increased. At seven through thirty minutes there was apparent supraventricular rhythm with right bundle block. The ventricular rate was more rapid than at control. P waves were not identified.

CASE 20. Auricular fibrillation with ventricular premature beats. The latter had almost disappeared at one-half minute. At ten minutes the supraventricular rhythm had a completely regular ventricular response (ventricular rate 64/minute). At fifteen minutes this was recognizable as an atrial tachycardia with 2:1 A-V block (128:64). The next day atrial fibrillation with ventricular premature beats was again present. Five days later (Fig. 3) the baseline curve was the same. At one minute the ventricular response increased from 94 to 140/minute with a short run of apparent sinus tachycardia (P-R interval = 0.16 second). At twenty minutes there was auricular fibrillation with short periods of auricular flutter. From thirty to ninety minutes 4:1 auricular flutter was observed. At one hundred

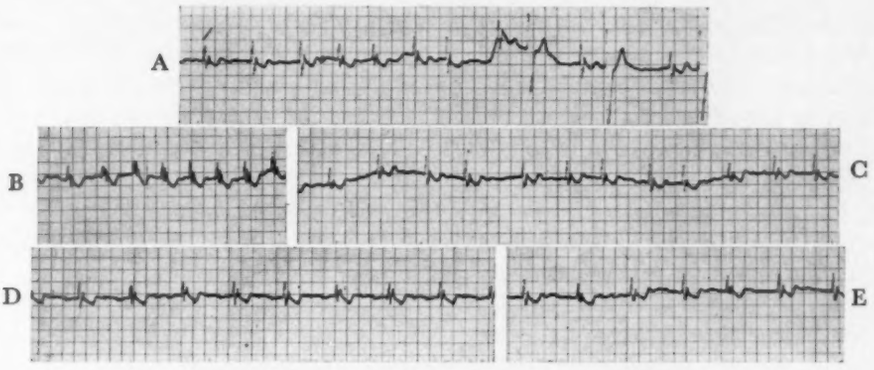

FIG. 3. Case 20. A forty-eight year old man who was digitalized. Lead V_2. A, control. Auricular fibrillation. Ventricular response 94/minute. Frequent ventricular extrasystoles. B, one minute after intravenous injection of 100 mg. Ro 2-5803. Ventricular response has increased to 140/minute. Last four complexes appear to have a P wave with a constant P-R interval (0.16 second). C, twenty minutes. Auricular fibrillation with short periods of auricular flutter. D, thirty minutes through ninety minutes. 4:1 auricular flutter. E, one hundred five minutes. Auricular fibrillation alternating with auricular flutter.

five minutes, the auricular fibrillation alternated with auricular flutter.

Blood Pressure Changes: There was no important change of the average systolic, diastolic and mean blood pressures. Hypotension was not observed.

Electrocardiographic Changes: A definite increase in the Q-T_e interval occurred at one minute after intravenous administration of 100 mg. of the drug. This effect is parallel to that observed in the group with sinus rhythm.

In four of eight patients definite slowing of measurable atrial activity occurred. In one patient, comparable slowing occurred during a repeat study. Therefore, in five of nine tests definite atrial slowing developed. Two of three patients with flutter reverted to sinus rhythm for a short period of time.

QRS complexes showed a slight but definite widening. Five of nine tests demonstrated an increased QRS. The contour of the QRS complex showed changes with widening of the complexes, such as broadening of the apex of the R, development of more discrete RrR′, RR′r″, etc. When increased widening occurred, the QRS contour changed from complex to complex for that period of time, with changing heights and depths of q, R, R′, S and S′ waves from beat to beat. Duration of QRS complexes increased an average of 0.01 second from baseline at one minute. Both patients with a QRS of greater than 0.10 second showed widening, whereas this occurred in but two of the six patients with a QRS of less than 0.10 second. This suggests that an increase of QRS duration is more likely to occur in patients with wider QRS complexes.

RS-T segments changed insignificantly as an average, although in one patient a slightly elevated S-T take-off became depressed 1 mm. below the baseline for three minutes.

T waves remained essentially unchanged in five of the nine tests. In two an increase of positivity occurred. In another, positivity was decreased from 2.5 mm. maximally at five minutes to 1 mm. In another, a diphasic T demonstrated an increase of negativity, maximally at one minute (−4 mm.).

ST-T segment changes were not remarkable on the whole.

Heart Rate: The ventricular rate increased after injection in six of nine tests, remained the same in two and decreased in one.

COMMENTS

In both groups of patients with the sinus rhythms and arrhythmias, a definite increase in the Q-T_e measurement occurred at one minute after the intravenous administration of 100 and (in one case) 150 mg. of Ro 2-5803. Some tendency to increased QRS duration was noted, perhaps more so where previous widening had existed, and in the group with fibrillation and flutter more than in the group with sinus rhythm. This is regarded as suggestive evidence that administration of drug tends to slow both depolarization and repolarization of the ventricles.

An increase in the ventricular rate was observed immediately after injection of the drug

in eleven of fourteen tests in patients with sinus rhythm and in six of nine tests in the group with flutter and fibrillation. When the atrial rates could be measured in the group with fibrillation and flutter evidence of slowing was found.

There was evidence that atrial flutter and fibrillation mechanisms may be converted. The rhythm in two patients with flutter and in one patient with fibrillation (two tests) changed to a sinus rhythm of short duration. In the latter patient there were also periods of conversion from fibrillation to pure flutter.

Transient heart block presumably due to digitalis intoxication was abolished in one patient. Ventricular premature contractions, when present, disappeared within one minute in all but one patient. There was suggestive evidence that this drug may prove of value in correcting some of the adverse effects of digitalis.

The fact that these changes were effected with doses of 100 mg. of Ro 2-5803 and that there were no serious side effects indicates the potential value of this drug in the management of arrhythmias.

There were no significant changes in blood pressure levels. This lack of hypotensive tendency after intravenous administration, if sustained at higher dosage levels, would offer a desirable contrast to the hypotensive action of quinidine and procaine amide.

Summary

A new drug possessing antifibrillatory activity in experimental animals and heart preparations on a par with quinidine was given intravenously to twenty-nine patients a total of forty-five times, in dosages beginning with 1 mg. and increasing to 150 mg.

No untoward effect or side reaction of the drug was observed at the dosage level used. Specifically, no hypotensive action was observed after intravenous administration at the dosage levels employed.

In causing an increase in the Q-T_e interval measurements immediately following administration and tending to increase QRS duration in some instances, the drug would appear to depress ventricular depolarization and repolarization.

When atrial activity could be measured in the group with fibrillation, definite atrial slowing was in evidence. In general, ventricular rates increased.

The drug demonstrated antiarrhythmic potential. Specifically, atrial flutter and fibrillation were converted to a sinus mechanism; fibrillation to flutter; A-V heart block and ventricular premature contractions were abolished.

In addition, the results suggest that Ro 2-5083 may be of value in reversing adverse rhythm effects due to digitalis.

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Preliminary Observations on a New Antiarrhythmic Agent (Ro 2-5803)*

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THE search for potent antiarrhythmic drugs continues despite the effectiveness of many agents which are currently in general use. There is a definite need for additional compounds with relatively low toxicity and with different limiting clinical and/or electrocardiographic characteristics than those possessed by the available antiarrhythmic drugs. Preliminary studies in animals with 2,6-bis (1-piperidylmethyl)-4-(α,α-dimethylbenzyl) phenol dihydrobromide (Ro 2-5803)† have indicated that this compound has significant ventricular and auricular antifibrillatory activity. The present report inquires into the clinical effectiveness of this drug.

PHARMACOLOGY

The efficacy of Ro 2-5803 against acetylcholine-induced auricular fibrillation in the dog has been determined,[1] and its antifibrillatory activity has also been tested on the isolated rabbit auricle by the Dawes method.[2] It was evident from both of these studies that Ro 2-5803 is at least as effective as quinidine in regard to its atrial antifibrillatory effect. Similarly, when pigs were subjected to a procedure of closed-chest coronary artery occlusion by which ventricular fibrillation was induced, potent antifibrillatory properties were also demonstrated by Ro 2-5803.[3] The chemical formula of the drug is illustrated in Figure 1.

MATERIAL AND METHODS

Thirty-four patients with a variety of auricular and ventricular arrhythmias were treated with Ro 2-5803 (Table 1). The drug was administered both intravenously and orally. Total parenteral dosage varied from 200 mg. to a maximum of 400 mg. Oral dosage varied from 100 to 400 mg. given four times a day (400 to 1,600 mg. daily).

Continuous electrocardiographic monitoring was performed in all patients in whom the drug was administered parenterally. Daily or frequent electrocardiograms were obtained in those subjects who received the oral medication.

RESULTS

Ventricular Arrhythmias: A summary of the results obtained with Ro 2-5803 is tabulated in Table 1. The drug was administered to fifteen patients with premature ventricular systoles. The response was excellent, i.e., normal sinus rhythm was restored in seven subjects; and the extrasystoles were decreased by at least 75 per cent in four others. However, in an additional four patients we failed to obtain any significant effect. One subject with paroxysmal ventricular tachycardia had a good antiarrhythmic response, i.e., the number of ventricular extrasystoles was decreased by at least 75 per cent. (It is of interest that administration of procaine amide and quinidine had previously failed to produce any antiarrhythmic effect on the latter patient.) In two others with paroxysmal ventricular tachycardia, response to oral administration of the drug was inadequate.

Atrial Arrhythmias: Normal sinus rhythm was restored in four of eight patients with

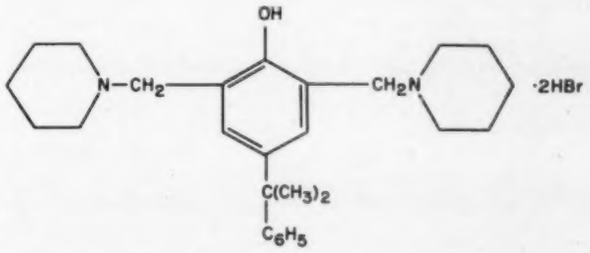

FIG. 1. Chemical formula of 2,6-bis (1-piperidylmethyl)-4-(α,α-dimethylbenzyl) phenol dihydrobromide (Ro 2-5803).

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† Ro 2-5803 was supplied by Hoffmann-La Roche, Inc., Nutley, New Jersey.

TABLE 1
Summary of Results with Ro 2-5803 in Thirty-four Patients with Cardiac Arrhythmias

Type of Arrhythmia	Patients Treated (no.)	Average Dose and Route of Administration	Results		
			Excellent*	Good†	Poor
Ventricular extrasystoles	12	100–400 mg. 4 times a day orally	6	4	2
	3	100–200 mg. intravenously	1	..	2
Auricular extrasystoles	4	200 mg. 4 times a day orally	1	1	2
Paroxysmal atrial tachycardia	1	200 mg. intravenously	1	..	..
Paroxysmal atrial fibrillation	4	200–400 mg. 4 times a day orally	3	..	1
	4	200–400 mg. intravenously	1	..	3
Paroxysmal atrial flutter	2	200-400 mg. intravenously	..	..	2
Paroxysmal ventricular tachycardia	3	200–400 mg. 4 times a day orally	..	1	2
Sinus tachycardia	1	400 mg. intravenously	..	..	1
Totals	34		13	6	15

* Restored normal sinus rhythm.
† Decreased extrasystoles at least 75 per cent.

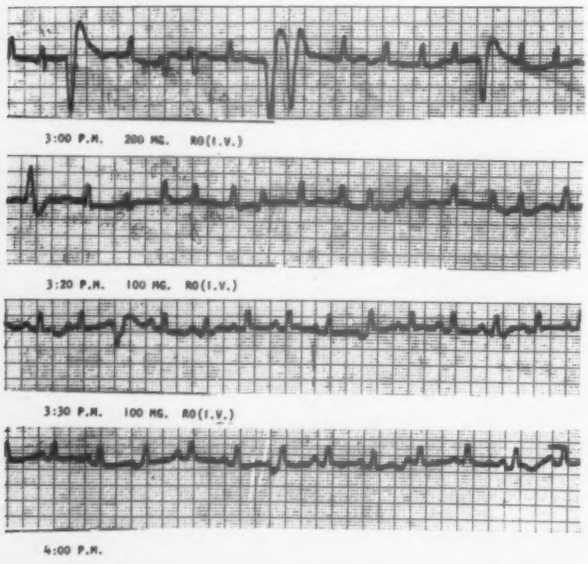

FIG. 2. The intravenous administration of 300 mg. of Ro 2-5803 converted the atrial fibrillation to normal sinus rhythm. An additional injection of 100 mg. also eliminated the ventricular premature systoles.

paroxysmal atrial fibrillation and in one patient with paroxysmal atrial tachycardia. In two of the four patients with atrial extrasystoles, improvement was also significant; however, in two subjects with paroxysmal

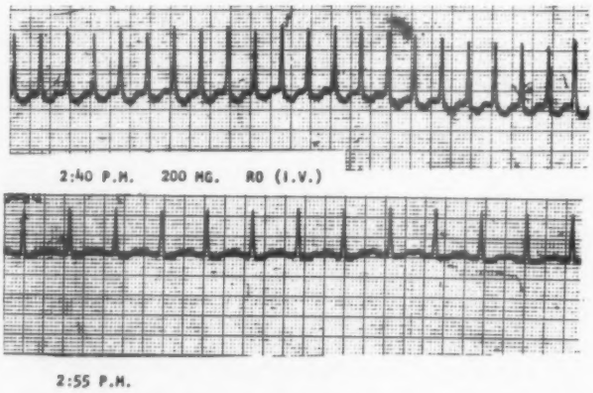

FIG. 3. Paroxysmal atrial tachycardia was rapidly converted to normal sinus rhythm by a single injection (200 mg.) of Ro 2-5803.

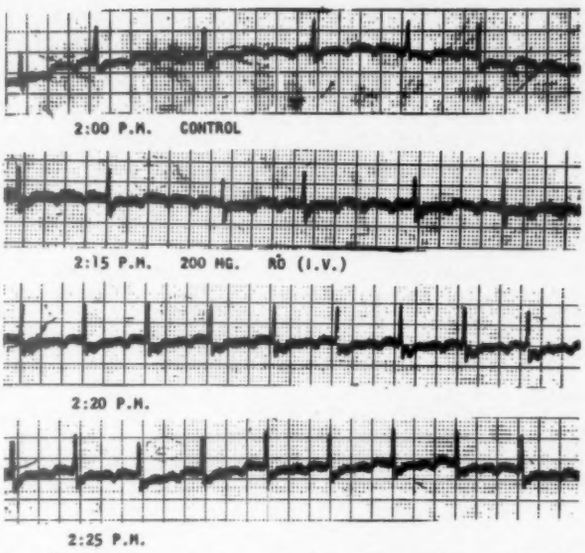

FIG. 4. The marked atrial depressive effect of Ro 2-5803 was demonstrated in this patient with atrial flutter in whom the atrial discharge was slowed from 240 to 180 per minute.

atrial flutter, we failed to obtain an antiarrhythmic response.

Side Effects: A widening of the QRS complex greater than 50 per cent occurred in two patients who received the drug intravenously, and the intraventricular conduction defect was associated with congestive heart failure in each. A total dosage of 400 mg. was infused over a twenty-minute interval in both of these subjects. The only other side effect encountered during parenteral administration was a feeling of warmth which frequently occurred during the intravenous infusion. Widening of the QRS complex did not occur with oral administration of the drug and other significant side effects were not encountered.

COMMENTS

Although Ro 2-5803 was not uniformly effective, the number of good results obtained was extremely encouraging. The effectiveness of the drug against ectopic atrial rhythms was demonstrated by the restoration of normal sinus rhythm in four patients with paroxysmal atrial fibrillation and in an additional subject with paroxysmal atrial tachycardia (Figs. 2 and 3). A marked atrial depressive effect was also observed in one patient with paroxysmal atrial flutter in whom the atrial rate was slowed from 240 to 180 per minute (Fig. 4).

Ro 2-5803 was also effective in the treatment of various ventricular arrhythmias. A significant reduction or complete disappearance of the extrasystoles was obtained in eleven of fifteen patients with ventricular premature systoles. In addition, one patient with chronic paroxsymal ventricular tachycardia (due to ateriosclerotic heart disease) was significantly relieved of his arrhythmia by the oral administration of the drug. The rapid disappearance of ventricular bigeminy in a patient with aortic stenosis who received Ro 2-5803 parenterally is demonstrated in Figure 5.

A significant widening of the QRS complex did not occur with the oral administration of the drug; and although widening of QRS complexes did occur with the parenteral administration, this effect would not appear

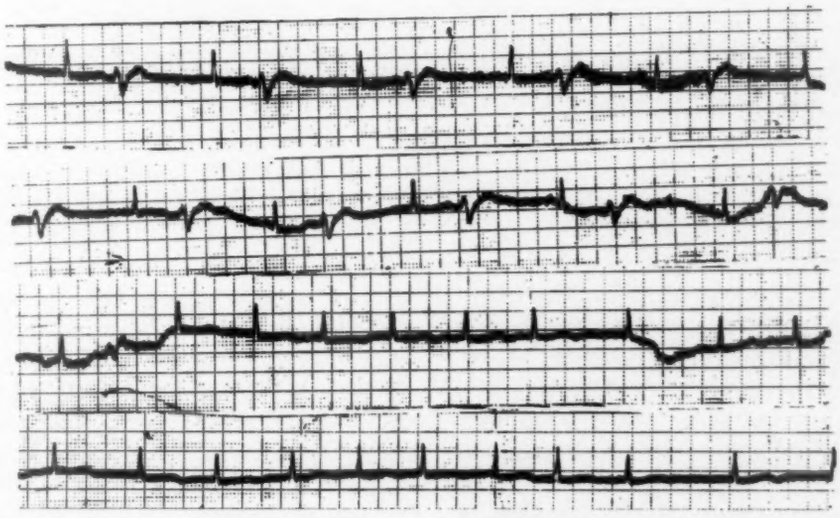

FIG. 5. Continuous tracing. The bigeminal rhythm was rapidly eliminated in this patient with aortic stenosis by the intravenous injection of 100 mg. of Ro 2-5803.

to be an absolute limiting factor. It is also significant that the number of associated side effects were few. Ro 2-5803 appears to be a potent antiarrhythmic agent with significant clinical potentialities. It is anticipated that further study will better define the ultimate role of this agent in the therapeutic management of atrial and ventricular arrhythmias.

Summary

The antiarrhythmic effect of Ro 2-5803 was investigated in thirty-four patients with various cardiac arrhythmias. The results obtained were excellent in thirteen patients in whom the drug restored and then maintained normal sinus rhythm. A good effect was achieved in an additional six patients in whom the frequency of extrasystoles was decreased by at least 75 per cent. In four patients with paroxysmal atrial fibrillation and in an additional patient with paroxysmal atrial tachycardia, normal sinus rhythm was restored. The incidence of side effects and untoward reactions was low.

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Reviews

Mitral Stenosis

Auscultatory and Phonocardiographic Findings*

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BEFORE discussing the auscultatory and phonocardiographic findings in mitral stenosis, it would be advantageous to summarize briefly the important physiologic changes that result from stenosis of the mitral valve. Our knowledge of these changes has been an outgrowth of the era of cardiac surgery and cardiac catheterization, and although all the signs and symptoms of this disease were known to clinicians over a century ago the significance of the findings was not known. Presently we are able to measure pressures and cardiac output, calculate the pulmonary vascular resistance and estimate the size of the mitral valve orifice.

By correlating the physical and auscultatory findings with knowledge obtained from catheterization studies and surgery we have learned much about the hemodynamic alterations in mitral stenosis, thus enabling us to predict accurately on clinical grounds alone valuable diagnostic and prognostic information. In many cases we may obviate the necessity of procedures which are uncomfortable to the patient, time consuming and which may even be associated with a significant morbidity.

Marked physiologic changes do not occur until the normal valve orifice (4 to 5 sq. cm.) has been reduced to a quarter of the normal or approximately to 1 sq. cm.[1-3] As a consequence of this, left atrial pressure rises sufficiently to compensate for the obstruction so that total mitral valve flow and cardiac output are normal or nearly normal. Greater degrees of narrowing cause higher left atrial pressures and reduced flow with a fall in the cardiac output.

The increased left atrial pressure leads to an increase in the pulmonary venous and capillary pressures, so that early in the course of mitral stenosis, pulmonary edema and hemoptysis are relatively common.[4] However, the persistent elevation in the pulmonary venous and capillary pressures eventually leads to arteriolar changes and an increase in the pulmonary vascular resistance and pulmonary artery pressure. The increased pulmonary vascular resistance is the most important physiologic consideration in mitral stenosis. Except for pulmonary edema and hemoptysis, most of the symptoms of mitral stenosis are a consequence of the increased pulmonary vascular resistance. High resistances lead to right ventricular hypertrophy and failure, a decreased cardiac output and, because of the associated parenchymal changes in the lung, decreased oxygen saturation; these sequelae explain most of the symptoms in patients with moderately severe and advanced mitral stenosis.[5]

In this review of the auscultatory abnormalities in mitral stenosis, we include our experience with over 150 cases proved by operation.

CLASSIFICATION OF AUSCULTATORY FINDINGS IN MITRAL STENOSIS

The following auscultatory and phonocardiographic findings in mitral stenosis will be reviewed in detail: (1) First sound: (a) accentuated mitral component (its variation in atrial fibrillation), (b) delayed mitral component (prolonged Q-1 interval) and (c) the tricuspid component of the first heart sound. (2) Second sound: (a) accentuated second sound and (b) reduplicated second sound. (3)

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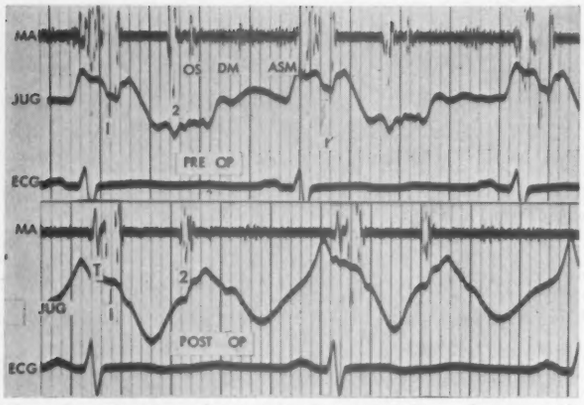

FIG. 1. Preoperative and postoperative phonocardiograms taken at the mitral area. The patient had a tight mitral stenosis with marked pulmonary hypertension of 150 mm. Hg. *Preoperatively*, the loud first mitral sound is delayed (Q-1 interval 0.12 second) and is preceded by an atriosystolic murmur. The second sound is accentuated and the 2-OS interval is 0.08 second; the opening snap (OS) is followed by a long diastolic murmur. *Postoperatively*, the first mitral sound is still accentuated and delayed. The tricuspid component of the first sound precedes the mitral component. The opening snap has disappeared. The presystolic and diastolic murmurs are markedly diminished. This patient had an excellent surgical result and is asymptomatic despite a persistent elevation of the pulmonary artery pressure.

SYMBOLS FOR ALL ILLUSTRATIONS

MA	= mitral area.
PA	= pulmonary area.
Erbs	= third left intercostal space.
Jug	= jugular venous pulse.
Car	= carotid artery pulse.
1	= mitral component of first heart sound.
T-	= tricuspid component of first heart sound.
2	= second heart sound.
2′	= pulmonary component of second sound when split.
3	= third heart sound.
OS	= opening snap.
SM	= systolic murmur.
DM	= diastolic murmur.
ASM	= atriosystolic (presystolic) murmur.
SC	= systolic ejection click.
A	= A wave of jugular pulse.
C	= C wave of jugular pulse.
V	= V wave of jugular pulse.
LF	= low frequency recording.
HF	= high frequency recording.

Opening snap of the mitral valve: (a) diagnosis and clinical significance and (b) the 2-OS interval. (4) Third heart sound. (5) The pulmonary ejection sound. (6) Systolic murmur: (a) apical systolic murmur and (b) pulmonary systolic murmur. (7) Diastolic murmurs: (a) mitral diastolic rumble, (b) atriosystolic murmur (presystolic murmur) and (c) basal diastolic murmurs: pulmonary insufficiency (Graham Steell) and aortic regurgitation (Austin Flint).

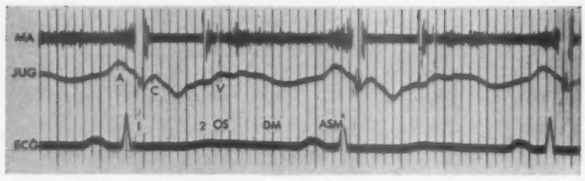

FIG. 2. *Mitral Stenosis.* The first sound is delayed (Q-1 interval 0.08 second) and accentuated and preceded by an atriosystolic murmur. The opening snap occurs 0.07 second after the loud second heart sound and there is a brief gap between the opening snap and the onset of the diastolic murmur which is decrescendo until the atriosystolic crescendo. The opening snap occurs at the peak of the V wave of the jugular venous pulse.

THE FIRST HEART SOUND

ACCENTUATED FIRST SOUND

The first sound in the mitral area is generally accentuated and of increased intensity. It also has a characteristically sharp, snapping or slapping quality, often is booming and accompanied by a palpable shock in the apical region. The phonocardiogram (Figs. 1, 2 and 3) confirms the striking increase in amplitude of the first sound in the mitral area as compared to that of the second sound.

The snapping first sound occurs in most patients with "pure" or advanced mitral stenosis but may be absent in those with mild stenosis and in those with predominant mitral insufficiency. It may also be absent in the presence of a calcified mitral valve regardless of the presence or absence of mitral insufficiency.

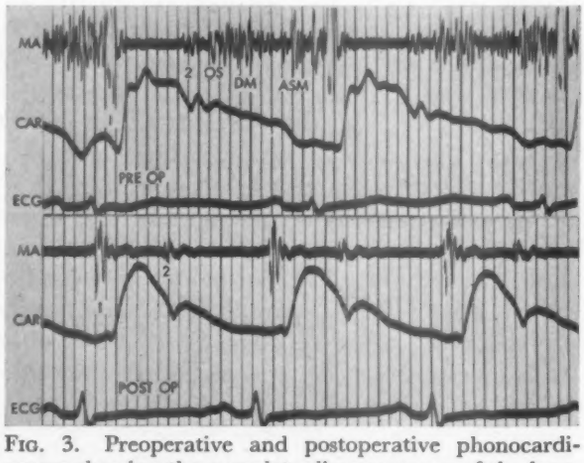

FIG. 3. Preoperative and postoperative phonocardiogram showing the complete disappearance of the long, low frequency diastolic and atriosystolic murmur and of the opening snap. The Q-1 interval which was 0.10 second preoperatively became shorter (0.08 second) postoperatively.

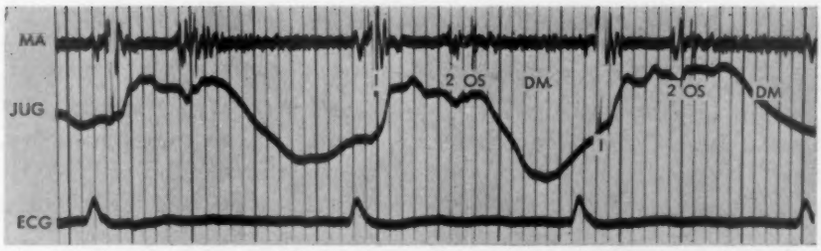

FIG. 4. The effect of atrial fibrillation on the intensity of the first sound, the Q-1 interval and the 2-OS interval. The second cycle follows a relatively long diastole and there is a moderately loud first sound, a Q-1 interval of 0.08 second and a 2-OS interval of 0.08 second. In the third cycle which follows a shorter diastole, the first sound is much louder, the Q-1 interval is (slightly) more prolonged (0.09 second) and the 2-OS interval is shorter (0.06 second).

Accentuation of the first sound may be the earliest sign of mitral stenosis and may occur in mild cases in patients with normal or only slightly elevated left atrial pressure. When atrial fibrillation appears the accentuation of the first sound becomes less marked.

Cause of Accentuated First Sound: The loud snapping first sound in mitral stenosis is probably produced by the increased tension of the mitral valve leaflets rather than by their rapid closure. Postmortem examination of such a diseased valve, as well as digital exploration during mitral commissurotomy, have demonstrated the valve leaflets to be thickened, sclerotic and scarcely able to close completely. There is a sufficient pressure gradient across the stenotic mitral valve to bellow the cusps deeply into the left ventricle and to prevent them from floating together during diastole until the moment when ventricular contraction occurs. This results in more forceful closure of the valve leaflets and a louder closing snap. The snapping quality of the first sound may be produced by increased tension specifically of the anterior cusp of the mitral valve. Direct auscultation of the heart during surgery has indicated that the snapping quality of the first sound disappears temporarily when the finger is placed on the anterior cusp as it balloons into the left atrium at the onset of ventricular systole.

Effect of Atrial Fibrillation: In the presence of normal sinus rhythm, atrial contraction results in accentuation of the first sound by further increasing the A-V pressure gradient in late diastole. In atrial fibrillation, however, atrial contraction ceases. There is variation in the intensity of the first sound from cycle to cycle. Normally the intensity of the first heart sound varies in atrial fibrillation according to the length of the previous diastole, being loudest when the diastole is short and diminishing in intensity as the diastole lengthens. However, there is a secondary increase in the intensity of the first sound when the diastole is longer than 0.25 second.[6] In mitral stenosis there may be no variation in the intensity of the first heart sound, especially if the stenosis is severe.[7] In other cases, however, there is an inverse relationship between the intensity of the first sound and the length of the previous diastole[8] (Fig. 4). The explanation afforded is based on the A-V gradient and the position of the mitral valves at the time of ventricular contraction. If the ventricle contracts early (short diastolic interval) the filling gradient is high, causing the mitral valve to be fully open and thereby producing a loud first sound. The converse is true with long diastolic periods.

Effect of Mital Insufficiency: When mitral insufficiency develops spontaneously or is produced by surgery, an accentuated first sound is not heard because the mitral incompetence results in early filling of the left ventricle during diastole and rapid decrease in the A-V pressure gradient. This may result in early floating into opposition of the thickened valve leaflets prior to ventricular contraction.

Effect of Mitral Commissurotomy: The accentuated snapping first sound is the auscultatory finding in mitral stenosis which is least affected by mitral valvulotomy unless mitral regurgitation has been produced.[9] Following mitral commissurotomy the intensity of the accentuated first sound may be significantly decreased in almost half the cases; generally this is evidence of a good operative result. However, the accentuated first sound may persist after a successful valvulotomy even when the rumbling diastolic murmur disappears or becomes less intense.[10] This is well seen in Figure 1 in which the diastolic murmur is

seen to have almost completely disappeared following valvulotomy but the first sound is still markedly accentuated, particularly the mitral component. Clinically, this patient had a good postoperative result. On the other hand, if the accentuated first sound becomes soft and of normal intensity it may indicate the postoperative development of significant mitral insufficiency and a poor clinical result.[4,9]

SPLIT FIRST SOUND

The first sound may be reduplicated in mitral stenosis. This is due to a true splitting of the sound rather than to the appearance of an additional sound in systole. The phonocardiogram indicates that the total duration of the two components generally equals the duration of a normal first sound, namely 0.10 to 0.13 second, but not infrequently it may be slightly prolonged. The splitting of the sound is produced by asynchronous closure of the A-V valves, probably due to delayed closure of the mitral valve.

Normally, the first major vibration of the first heart sound is caused by closure of the mitral valve.[11] The tricuspid valve closes within the next 0.02 to 0.03 second unless there is complete right bundle branch block, in which case the tricuspid component may be delayed an additional 0.03 second.[12] In mitral stenosis closure of the mitral valve is delayed and may occur as late as 0.12 second after the onset of the QRS.[13] In such instances the closure of the tricuspid valve is earlier, and audible splitting of the first sound rarely may result. However, in the majority of cases the presystolic murmur or the markedly accentuated and delayed mitral valve closure causes the fainter tricuspid sound to be unappreciated. For this reason, audible splitting is not a common finding although in viewing the phonocardiogram one might expect the converse.

DELAYED FIRST SOUND

The onset of the first sound in the mitral area is often delayed in mitral stenosis[13] (Figs. 1 through 4). This may be difficult to demonstrate owing to the wide variation in the length of the interval from the beginning of the QRS to the onset of the first sound (Q-1 interval) in normal subjects as well as in those with mitral stenosis. In normal tracings the first sound may start from 0.02 to 0.06 second after the beginning of the QRS. As a general rule, the initial major vibrations of the first sound begin within 0.05 or at most 0.06 second after the onset of the QRS. An increase of the Q-1 interval to 0.07 second or more indicates delayed onset of the first sound. The sound may be so delayed that the initial major vibrations occur after the end of the QRS. The maximal vibrations as well as the initial vibrations are also delayed.

Several authors[14–16] have attempted to correlate the degree of delay in mitral valve closure with the severity of the mitral stenosis. However, Wells[14,17] found a delay in only fifty-one of one hundred cases of mitral stenosis. It has been observed also that a delayed first sound is not pathognomonic of mitral stenosis. Thus, Weissler et al.[18] noted a significant delay in mitral valve closure in a group of hypertensive patients. Other factors, such as the length of the P-R interval during sinus rhythm and the length of the preceding diastole during atrial fibrillation, play a role in the determination of the degree of delay of mitral valve closure. The Q-1 interval delay therefore is a common finding in mitral stenosis, but it is not a specific finding and is of little value in assessing the severity of an individual case.

The Components of the First Sound: Accurate timing of the onset of the first sound is rendered difficult by the presence of a late diastolic or crescendo presystolic murmur which may merge with the onset of the first sound (Fig. 1). Although the onset of the initial vibrations is obscured by the presystolic or late diastolic murmur, it may be evident that the maximal vibrations of the first sound (second component) are delayed beyond 0.06 second after the onset of the QRS, as is seen in Figures 1 through 4

In the absence of late accentuation of the diastolic murmur of mitral stenosis, it is possible to analyze the character and timing of the first sound more accurately. It then may be seen that the first sound in mitral stenosis is comprised of two components. The first component is composed of several low frequency vibrations which begin normally 0.02 to 0.04 second after the onset of the QRS and last for 0.04 to 0.06 second. These are of low intensity as well as of low frequency and usually are not audible during routine auscultation. They are visible only in the phonocardiogram recorded with the low frequency microphone. This component is followed by the second component of the first sound which is composed of high frequency vibrations of high amplitude and intensity. The second component is identified by the

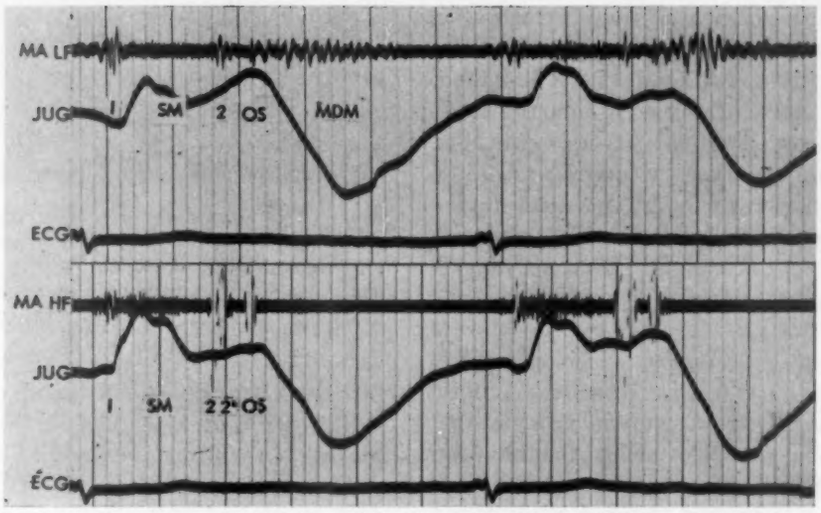

FIG. 5. Predominant mitral stenosis with mitral regurgitation. *The low frequency recording above* shows a mid-diastolic murmur preceded by an opening snap. There are low frequency vibrations preceding the onset of the first heart sound despite the presence of atrial fibrillation. *In the high frequency recording below*, a split second sound is recorded, the opening snap is of greater intensity but the diastolic murmur is recorded only in early diastole. It also demonstrates the high frequency systolic murmur best.

ear as the accentuated first sound and identified on the phonocardiogram as the delayed loud first sound.

The initial low frequency vibrations of the first sound are visible even in the presence of atrial fibrillation[19] (Fig. 5). Therefore, this component cannot be attributed to atrial contraction alone and does not correspond to the normal atrial component of the first sound. It is possible that it is produced by myocardial contraction at the onset of the isometric phase of ventricular systole and is recorded before closure of the mitral valve. However, this remains unproved and it may be due to earlier closure of the tricuspid valve (Figs. 1 and 6). The early low frequency component is generally obscured and included within the presystolic murmur when the latter is present. The second valvular component of the first sound is generally distinct from the end of the presystolic murmur.

The delay in onset of the first sound indicates delayed closure of the mitral valve. The latter has been attributed to incomplete filling of the left ventricle during diastole as a result of the reduced blood flow through the stenotic mitral valve.[20] Impaired and incomplete left ventricular filling results in a disturbance in the normal pressure gradient between the left atrium and ventricle (A-V gradient) which determines the time of onset of mitral valve closure. An increase in the normal A-V pressure gradient results in delayed closure of the mitral valve.

Tricuspid Component of the First Sound: It has been pointed out[7,21] that the tricuspid component of the first sound often can be identified on the phonocardiogram but because it is of low frequency and low amplitude it normally remains inaudible. It is recorded most consistently over the tricuspid area and occurs from 0.05 to 0.07 second after the onset of the QRS complex. It coincides with the onset of the pressure rise in the right ventricle.[7,21] The intensity of the tricuspid valve closure varies inversely with the length of the preceding diastole. It is important to recognize closure of the tricuspid valve especially when utilizing the Q-1 interval as a guide to the severity of the stenosis because it may be erroneously

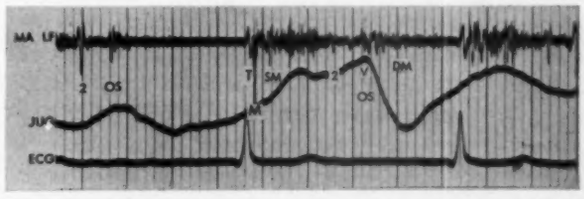

FIG. 6. *Combined mitral stenosis and regurgitation.* Both the tricuspid and mitral components of the first heart sound are clearly identified. There is a moderately loud holosystolic murmur. The 2-OS interval is 0.13 second. The mid-diastolic murmur ends before the succeeding first sound without a presystolic accentuation because of the presence of atrial fibrillation. The opening snap coincides with the peak of the V wave.

interpreted as the closure of the mitral valve in which case the Q-1 interval would be more normal. In addition, rather than the so-called muscular component of the first heart sound, closure of the tricuspid valve may be responsible for the low frequency vibrations noted preceding the mitral component in patients with atrial fibrillation. Loud closure of the tricuspid valve has been considered to be one of the mechanisms that simulates the presystolic murmur of mitral stenosis.[22]

Effect of Atrial Fibrillation: The delay in onset of the first sound has been observed more commonly in the presence of atrial fibrillation, particularly when the preceding diastole has been very short.[8,23,24] Correlation of the Q-1 interval with the length of the preceding diastolic cycle has shown an inverse relationship between these two intervals. These observations also suggest a slight delay in left ventricular contraction and mitral valve closure due to incomplete ventricular filling. During a short cycle, ventricular filling is affected even more than in the longer cycles and the delay in mitral valve closure may be greater. As previously shown, this relationship between cycle length and ventricular filling may also influence the intensity of the first sound.

Second Heart Sound

Splitting of the Second Sound: Normally, the second sound may be split as much as 0.08 second on inspiration, but on expiration the split narrows so as to be inaudible.[25] Fixed splitting even on expiration occurs only with large left-to-right shunts, pulmonary stenosis and in right bundle branch block. Therefore, to detect abnormal splitting one should listen in expiration and at the pulmonary area.

In assessing the second heart sound in mitral stenosis one must be aware that normally only the aortic component is heard at the mitral area unless the pulmonary component is markedly accentuated. In addition, if mitral regurgitation is present the pansystolic murmur may bury the aortic component at the mitral area; if aortic stenosis is present closure may be inaudible. Therefore, analysis of the second sound in the mitral area may be difficult and misleading. One should evaluate the second sound in the pulmonary area because the pulmonary component is best heard there and in fact may be audible only in that location. In mitral stenosis, splitting is usually of normal degree unless there is right bundle branch

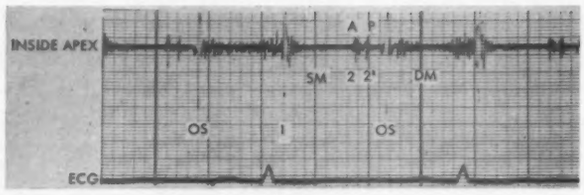

Fig. 7. The presence of a split second sound and an opening snap is illustrated. The opening snap is the loudest sound in the cardiac cycle. There is a decrescendo diastolic murmur followed by an atriosystolic murmur. A soft mid-systolic murmur is also present.

block. Contrary to a common belief, wide splitting is not a feature of pulmonary hypertension in mitral stenosis.[26] In fact, in the presence of pulmonary hypertension the splitting is narrow and not fixed. Of greater importance is the accentuation of the pulmonary component which is caused by increased pulmonary pressure.

In the graphic tracings the second component begins 0.01 to 0.05 second after the first component with an average gap of 0.03 second.[27] The combined duration of the two components may reach 0.09 second. They may be of equal intensity or amplitude or one may be distinctly accentuated. Generally, the second component is loudest in the pulmonic area.

If one listens carefully over the pulmonary area the splitting will become more evident on inspiration and less marked during expiration. On inspiration frequently one can identify the aortic and pulmonary components followed by the opening snap (Fig. 7). The latter is frequently mistaken for the pulmonary component and affords an explanation for the erroneous conception that wide splitting is common in mitral stenosis. An apical third sound is rarely transmitted to the pulmonary area and therefore would seldom be misinterpreted as a delayed pulmonary second sound.

The phonocardiogram is of distinct aid in documenting the clinical impression or in helping the clinician evaluate the sounds at the base of the heart. The jugular venous pulse tracing recorded simultaneously usually shows the reduplicated sound occurring at the hooking (crochetage) of the venous pulse or onset of the V wave[28] (Fig. 2), whereas the opening snap occurs at the peak and the third sound on the descending limb of the V wave.[29] Carotid artery tracings reveal that as in the normal the earlier component of the second sound is aortic and the later component is pulmonic.

Correlation with Hemodynamic Measurements: Catheterization studies have indicated that there is a fairly close correlation between the pulmonary artery pressure and pulmonary vascular resistance on the one hand, and the intensity and degree of splitting of the pulmonary second sound on the other.[4] The most marked accentuation and least reduplication of the pulmonary second sound is observed in patients with the most marked pulmonary hypertension and increased pulmonary vascular resistance. A normal pulmonary second sound is generally associated with a normal pulmonary artery pressure. It is of interest that the accentuation or splitting of the second pulmonic sound is generally not affected by mitral valvulotomy, even when the functional result is good and pulmonary artery pressure is reduced.

The aortic component is not uncommonly faint over the aortic area. The explanation for this is not positively known. With severe mitral stenosis the cardiac output may be diminished, thus lowering the aortic pressure and decreasing the intensity of the aortic second sound. Also, rotation of the heart in a clockwise direction may swing the aorta toward the left sternal border and cause aortic closure to be more distant.

Opening Snap of Mitral Valve (Mitral Click)

Ever since the nineteenth century when the auscultatory findings of mitral stenosis were first recognized, clinicians have noted a typical triple rhythm which was labeled by various descriptive terms, such as "bruit de marteau" or "bruit de rappel" because it sounded like a hammer or drum.[30] Duroziez[31] likened the familiar cadence to the syllables "ffrous-ta-ta-rrou." These early observers attributed the triple rhythm to a wide splitting or reduplication of the second heart sound produced by asynchronous closure of the semilunar valves, but later clinicians[32,33] believed that it was produced by vibrations in the stenotic mitral valve.

We now recognize that this triple rhythm is a succession of the two normal heart sounds and an additional sound at the onset of the diastole. This additional sound may be a reduplicated second sound, an opening snap of the mitral valve (mitral click) or accentuated physiologic third sound. One or more of these three types of triple rhythm may be detected in most cases of mitral valve disease. Potain and Rouches[34] first introduced the term which is commonly used today to describe the mitral click, namely "claquement d' ouverture de la mitrale" or opening snap of the mitral valve. The nature and exact moment of production of this sound has been elucidated by modern phonocardiography and pulse tracings,[35–37] which have confirmed that the opening snap or mitral click occurs at the time of opening of the stenotic mitral valve.

Auscultatory Characteristics: The opening snap is audible and recorded in the majority of patients with mitral stenosis.[4] Its incidence has been estimated to be as high as 85 per cent. In one large series of 150 cases of "pure" mitral stenosis proved by surgery, it was present in all but two cases.[4] Occasionally, it is not audible but may be recorded in the phonocardiogram.

It can be described as a snapping or clicking sound which follows the second sound by a short interval. In some cases its intensity may exceed that of the second sound and occasionally even that of the first sound (Fig. 7). It is generally loudest medial to the mitral area, in the supramammary area and over the lower left sternal border. Not infrequently, it is transmitted upward and may be prominent in the pulmonic area. In fact a triple rhythm in the pulmonic area is generally due to an opening snap more often than to reduplication of the second sound. Often both may be present in the same patient (Fig. 7).

The opening snap is best heard in the recumbent position in expiration and may be elicited or accentuated by exercise or increase in heart rate. When a protodiastolic murmur of mitral stenosis is present, it generally begins immediately or soon after the opening snap (Fig. 1). A short silent gap may be present between the opening snap and the diastolic murmur (Fig. 2). In many instances it is impossible to separate the initial vibration of the diastolic murmur from the preceding opening snap and the presence of the latter can be recognized only in the phonocardiogram (Figs. 3 and 6). This is true also in the occasional case in which the snap is soft or of low amplitude.

Phonocardiographic Features: In the phonocardiogram the opening snap is a fairly high-pitched vibration of short duration, which resembles in appearance the second heart sound. It generally consists of one to five rapid vibrations which last for 0.02 to 0.05 second (average duration 0.03 second). Their frequency range is generally between 25 and 100 per second, approximately the same as that of the second

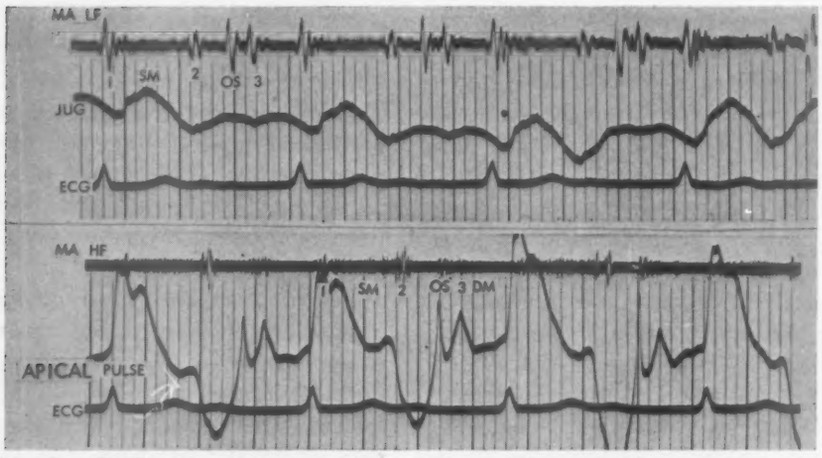

FIG. 8. *Combined mitral stenosis and regurgitation.* There is both an opening snap and a third heart sound at the apex. The apical pulse tracing below demonstrates a sharp peak occurring at the time of the opening snap.

sound.[27] Occasionally, the mitral click consists of only one or two vibrations.

Apex Beat Tracing: The superficial clicking vibration produced by the mitral opening snap may be transmitted to the chest wall and become evident as a palpable shock or impact over the precordium in early diastole. This may be identified in the graphic tracing of the apex beat as a sharp upward deflection of the curve after the end of the ventricular systole (Fig. 8). Following this there may be seen the transmitted vibrations of the mid-diastolic murmur and thrill.

SECOND SOUND-OPENING SNAP INTERVAL

The position of the opening snap in relation to the second sound is variable. The interval between the onset of the second sound and the mitral click (2-OS interval), which is equivalent to the isometric phase of diastole, ranges from 0.03 to 0.14 second.[37] There may be considerable variation in duration of this interval with the heart rate, the interval becoming shorter as the rate increases and the length of the cardiac cycle decreases. In the presence of atrial fibrillation or marked sinus arrhythmia, the duration of the isometric phase varies with the length of the preceding cardiac cycle, the opening snap occurring earlier when the diastolic interval is shorter, and later when the preceding cardiac cycle is longer[15,16] (Fig. 4).

This correlation between cycle length and 2-OS interval in any individual case has been attributed to variation in ventricular filling and A-V pressure gradient with changes in cycle length.[38] Thus, when the preceding cardiac cycle has been short, atrial emptying has been insufficient and left atrial pressure rises. This produces an increased A-V pressure gradient earlier in the subsequent diastole and therefore earlier opening of the mitral valve and an earlier mitral snap.

DIFFERENTIAL DIAGNOSIS OF OPENING SNAP

The opening snap or mitral click can be best identified by correlation of the phonocardiogram with the jugular venous pulse tracing (Figs. 2 and 9). Such correlation indicates that the opening snap occurs slightly before or simultaneously with the summit or peak of the V wave,[29] which marks the opening of the A-V valves and onset of the inflow of blood from the atria into the ventricles.

In reduplication of the second heart sound (Fig. 10) the second component is recorded simultaneously with the ascending limb of the V wave and precedes the peak. The interval between the two components is shorter than the 2-OS interval, ranging from 0.01 to 0.05 second, but considerable overlapping may occur. Not infrequently, a split second sound and a mitral snap are recorded in the same individual (Figs. 5 and 7). The interval between the two components of the split sound, unlike the 2-OS interval, may be affected considerably by deep respiration, becoming longer during deep inspiration.

An accentuated third sound is recorded simultaneously with the descending limb of the V wave, during the early rapid inflow of diastole (Fig. 8). The third sound is lower pitched, softer and occurs later in diastole than the opening snap. The interval between the beginning of the second sound and the onset of the third

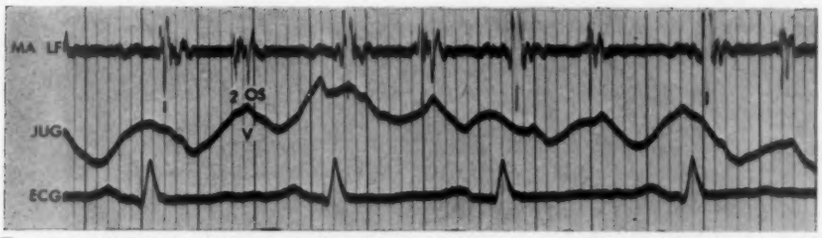

FIG. 9. *Tight mitral stenosis with pulmonary hypertension.* The Q-1 interval is 0.10 second. The first heart sound is moderately accentuated. The 2-OS interval is very short (0.04 second). Identification of the opening snap is aided by the jugular venous pulse tracing. A diastolic murmur was not present in this patient despite the existence of tight mitral stenosis.

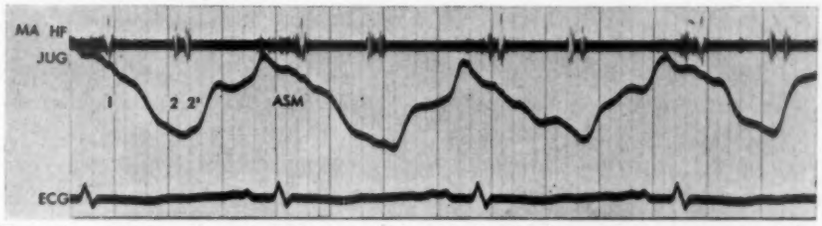

FIG. 10. *Effect of heavy calcification of the mitral valve* (proved at autopsy). The first heart sound is not accentuated. There is moderate splitting of the second sound. No diastolic murmur is present but instead there is a high-pitched, high frequency atriosystolic murmur. An opening snap is not present.

sound ranges between 0.12 and 0.2 second.[39] Some overlapping of the 2-OS and S_2-S_3 interval occurs.

Limitation of Venous Pulse Curve: Although the simultaneous recording of the jugular venous pulse and phonocardiogram is of great aid in identifying the additional sound in early diastole, the method is not without error. This is due to considerable variation in the position of the additional sound with reference to the V wave in different subjects and even in the same subjects from cycle to cycle. Thus, we have observed cases in which the opening snap preceded the peak of the V wave and other cases in which a third sound occurred simultaneously with the peak of the V wave. This suggests that there may be a delay in the recording of the venous pulse tracing, particularly when a mechanical rather than electrical technic for recording is employed.

Another cause for the discrepancy is the fact that the venous pulse curve reflects events in the right side of the heart whereas the opening snap and third sound are produced predominantly by events in the left atrium and ventricle. Asynchronism between mitral and tricuspid valve movements will result in asynchronism in the phonocardiogram and venous pulse tracing. A third cause for disturbed correlation between these two graphic tracings is the possible presence of functional or organic tricuspid insufficiency, which may produce distortion of the venous pulse curve and possible delay in the onset of the V wave.

CAUSE AND CLINICAL SIGNIFICANCE OF OPENING SNAP

The opening snap is thus a result of the structural changes within the mitral valve which lead to stiffening and rigidity of the leaflets, and of the increased A-V pressure gradient in early diastole. The most generally accepted explanation at the present time is that the opening snap is valvular in origin and is produced by sudden limitation of the opening movement of the stenotic mitral valve leaflets in early diastole, producing an audible vibration. Others have attributed it to the abrupt backward billowing of the mitral valve leaflets into the left ventricle when the left ventricular pressure drops below left atrial pressure at the end of the isometric phase of diastole.[4]

It has been suggested that, like the accentuated and delayed first sound, the opening snap is produced mainly by vibration of the aortic cusp of the mitral valve. For this reason, mitral insufficiency or aortic insufficiency may prevent the mitral snap by interfering with the backward movements of the aortic cusp of the mitral valve. This explains the less constant opening snap in mitral stenosis combined with mitral or aortic insufficiency.

On the other hand, the combination of an accentuated first sound and loud opening snap speaks for an advanced degree of mitral stenosis.

Disappearance of the opening snap occasionally may be observed following successful mitral commissurotomy (Fig. 1) but in the majority of cases the opening snap persists (Fig. 11). In many cases the 2-OS interval has been lengthened appreciably after successful surgery.[15]

Diagnostic Significance: The recognition of the opening snap in cases of mitral valve disease is important for diagnosis and estimating prognosis. Firstly, not infrequently a well defined snap may be present but the diastolic or presystolic murmur is faint and barely audible or even absent entirely. This is true particularly after atrial fibrillation develops, when the presystolic murmur disappears but the mitral snap remains. An opening snap may be the first clinically recognizable sign of mitral stenosis but by itself affords no information as to the severity of the lesion.

The interval between the onset of the second heart sound and opening snap, however, is of some prognostic importance in assessing the severity of the stenosis. The duration of the interval is dependent upon the left atrial pressure.[15,16] With high mean left atrial pressures, the mitral valve opens earlier in a diastole and hence the 2-OS interval is short (Fig. 9). Low left atrial pressures result in a later opening of the mitral valve and a long 2-OS interval (Fig. 7). Wells,[16] Kelly[15] and others have shown a good correlation exists between the 2-OS interval and the severity of the stenosis. An even better correlation was shown to exist when the Q-1 interval minus the 2-OS interval was used.[16] If the Q-1 minus the 2-OS was minus 1 or more positive it signified severe stenosis. If it was more negative than minus 1.5 then the mitral valve orifice proved to be greater than 1 sq. cm. at operation, and stenosis was not severe.

The intensity of the opening snap is dependent on several factors and of itself gives no information as to the severity of the stenosis. Also, an opening snap may be present even when mitral regurgitation is the dominant lesion; therefore, valvulotomy should not be performed solely on the basis of an audible opening snap.

Mitral Valve Calcification: In extremely advanced mitral stenosis, when the valve leaflets are deformed, rigid and matted down, the opening snap may become faint or even disappear because of the loss of suppleness and ability of the valves to snap together. This is true particularly when calcification of the valves develops. Wynn[40] found a distinct relationship between the absence of an opening snap and of accentuation of the first sound and the presence of calcification of the mitral valve. He postulated that the calcified leaflets lose their ability to snap shut and open at the onset of systole and diastole. This is not an absolute correlation, since an opening snap may be recorded in at least 50 per cent of the patients with proved mitral valve calcification. In general, however, the absence of a mitral click in the presence of a loud rumbling diastolic murmur is suggestive but not indicative of mitral valve calcification.

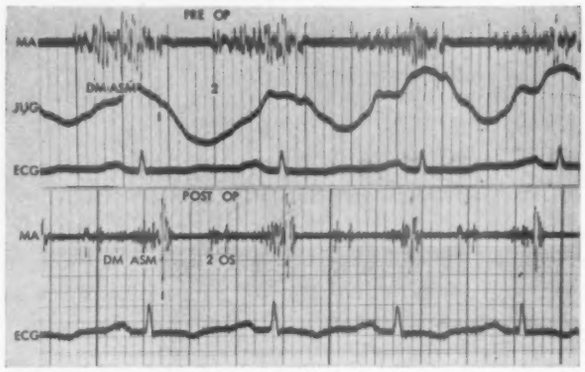

FIG. 11. Preoperative and postoperative phonocardiogram demonstrating some diminution in intensity of the diastolic and atriosystolic murmur, but with the persistence of all of the auscultatory characteristics. Despite this, a good functional result was obtained.

Mitral Insufficiency: Dominant mitral insufficiency is another cause for the absence of a well defined opening snap in the presence of other auscultatory findings of mitral stenosis. Mitral insufficiency prevents the opening snap because there is free filling of the left ventricle as in a normal heart, or because the valve leaflets are too rigid or deformed to allow them to snap open as the A-V pressure gradient is reversed at the onset of ventricular diastole.

Pulmonary Hypertension: An additional cause for the absence of a mitral click in advanced cases of mitral stenosis has been found to be an extremely high pulmonary vascular resistance.[4,41,42] This is difficult to explain since three-fourths of such patients exhibit a high left atrial pressure and an audible opening snap. Its absence can possibly be attributed to a large pulmonary artery and right ventricle which may dampen the intensity of the sounds

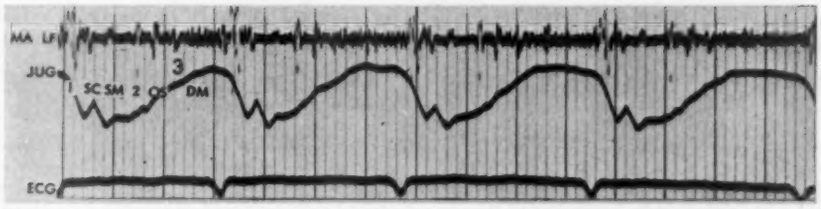

FIG. 12. There is both an opening snap and third heart sound recorded at the mitral area in this patient with *predominant mitral stenosis but with minimal regurgitation.* The first sound is loud and delayed and there is a systolic ejection click following the first heart sound.

produced by the aortic cusp of the mitral valve. Clockwise rotation of the heart may displace the left ventricle posteriorly so that the click may not be audible at the usual mitral area, but only audible in the mid or even posterior axillary line. It has been pointed out that with associated aortic regurgitation an opening snap may be absent.[4] In addition, the stroke output is diminished in pulmonary hypertension and thus may account for an absent opening snap.

Pulmonary Ejection Sound

An early systolic sound may be recorded over the pulmonary area but it is rarely audible in mitral stenosis (Fig. 12). This has been termed the pulmonary ejection sound by Leatham and Vogelpoel.[44] They demonstrated that it occurs on the average of 0.14 second after the onset of the QRS and after the rise in pulmonary artery pressure. It is therefore related to ejection of blood into the pulmonary artery. Sudden distention of the pulmonary valve annulus or pulmonary artery is probably the mechanism of its production.[43,44] The early pulmonary ejection click occurs in cases of pulmonary hypertension of any cause, pulmonary stenosis and dilatation of the pulmonary artery due to left-to-right shunts.[44,46] In mitral stenosis it was recognized in fifteen of twenty phonocardiograms but audible in only seven cases in the series of Leo and Hultgren.[7] It probably signifies dilatation of the pulmonary artery due to pulmonary hypertension in this group of patients.

Third Heart Sound

Since the third heart sound occurs during the rapid inflow phase of diastole and since early diastolic ventricular filling is usually impeded by mitral stenosis, a physiologic third sound would not be expected to occur in pure mitral stenosis. This is generally true, for the third sound is absent or of diminished intensity unless there is associated mitral insufficiency. The presence of a loud third sound confirmed by a phonocardiogram should suggest the presence of associated mitral insufficiency although it may be caused by tricuspid regurgitation.[46] In a recent study[4] it was found that a third heart sound was never present unless there was an associated loud systolic murmur suggesting mitral insufficiency or a significant degree of mitral insufficiency was palpated by the surgeon during valvulotomy.

Differentiation of Third Sound and Opening Snap: Another reason for accurate identification of the third sound when it is present, is the importance of differentiating it from the opening mitral snap. An opening snap would indicate mitral stenosis whereas a third sound would suggest mitral insufficiency. On auscultation the third sound is generally dull and of lower pitch and occurs later in the diastolic phase than the opening snap. It does not have the sharp snapping quality of the latter. On the phonocardiogram the third sound is a low frequency vibration and its mid-point occurs approximately 0.12 to 0.24 second after the beginning of the second sound as compared to a range of 0.03 to 0.14 second for the opening snap[39] (Fig. 8). As far as its location is concerned, the third sound is generally best heard and recorded at the apex of the heart or just medial to the mitral area, whereas the opening snap is louder within the apex or at the left sternal margin.

Diagnostic and Prognostic Significance of Third Sound: It is evident that the recognition of a loud third sound in patients with mitral stenosis is of great practical importance, because of its association with significant mitral insufficiency. It should be realized, however, that rarely a third sound is heard with predominant mitral stenosis and an opening snap is present when insufficiency is the dominant lesion. Its presence also should suggest the possibility of mitral regurgitation even in the absence of a systolic murmur.

Experience has indicated that patients with a prominent third sound often do not do well following valvulotomy since they have combined mitral stenosis and insufficiency, and valvulotomy for the mitral stenosis may aggravate the insufficiency. A third sound present preoperatively rarely disappears postoperatively even if a good functional result is obtained. On the other hand, a third sound may appear for the first time postoperatively, suggesting the development of some degree of mitral insufficiency. For these reasons Wood has gone so far as to recommend that valvulotomy for mitral stenosis should not be performed when a loud third sound is detected prior to surgery.

Systolic Murmur

Systolic murmurs of varying location, intensity and character are common in patients with mitral stenosis even in the absence of significant organic mitral insufficiency.

SYSTOLIC APICAL MURMUR

An early systolic murmur of grade 1 to 2 intensity may occur in pure mitral stenosis (Figs. 5 and 7).[47] Occasionally, the murmur may be of grade 3 intensity or louder. It may be blowing or harsh in character. It begins immediately after the first sound and occupies the first half of systole. It differs from the systolic murmur of mitral insufficiency which generally is loud (grade 3 or more), prolonged, fills the entire systole (holosystolic), is accentuated in late systole and fuses with the second sound.

Clinical Significance: The significance of the apical systolic murmur is not clear. It may be produced by previous acute rheumatic carditis which results either in sclerosis and dilatation of the mitral ring or dilatation of the left ventricle. It may also be due to a mild degree of associated mitral insufficiency which may not be clinically recognizable. It is possible that regurgitation of a small amount of blood through a narrow orifice at high pressure may produce a fairly loud systolic murmur without other signs of significant regurgitation. In a patient with such a systolic murmur, digital palpation of the valve by the surgeon during commissurotomy may reveal no palpable regurgitant jet. As a general rule, however, when a pansystolic murmur of grade 3 intensity or more accompanies the diastolic murmur of mitral stenosis, it is fairly safe to assume that it is produced by mitral insufficiency, but the severity of the latter cannot be estimated from the murmur alone.[4,47]

Other Causes for Apical Systolic Murmur: Another cause for a pansystolic apical murmur is tricuspid regurgitation.[48] Not infrequently, due to right ventricular enlargement, the systolic murmur of tricuspid regurgitation is louder at the apex than over the left fourth intercostal space. The timing and characteristics of this murmur may be identical with those of mitral insufficiency and operation for mitral stenosis may be denied solely on the presence of the murmur. One method of differentiation from mitral insufficiency is intensification of the tricuspid regurgitant murmur on deep inspiration although this is not invariably observed.

The ejection systolic murmur of aortic stenosis is occasionally louder at the apex than over the aortic area. However, the timing characteristics of the murmur are preserved, being midsystolic and therefore commencing after the first sound and ending distinctly before the second sound.

Surgical Indications in Presence of a Systolic Murmur: The presence of an apical systolic murmur even in the absence of other signs of mitral insufficiency may make a decision for or against mitral valvulotomy difficult. The observations of most surgical groups indicate that an apical systolic murmur can occur in the absence of detectable mitral regurgitation. Thus, in one group of sixty-one patients in whom the surgeon could detect no palpable regurgitant jet at operation, an apical systolic murmur was present in thirteen.[49] A systolic murmur was always present when the valve orifice was wide and rigid, indicating insufficiency, but it was only of grade 2 intensity in one of these patients. Even a loud murmur may not be an indication that the valve is unsuitable for surgery, for in one of the patients in this series with a grade 4 systolic murmur the valve at operation proved to have a small orifice with supple cusps and no regurgitation. It was also noted that there was no particular character of the systolic murmur which was associated with a valve deemed to be unsuitable for surgery.

On the other hand, the presence of a grade 3 or 4 systolic murmur is of great diagnostic importance, since a moderate or severe degree of mitral insufficiency, as determined by the direct palpation of the valve during surgery, was present in 70 per cent of such patients. The remaining 30 per cent of the patients had no or only minimal mitral insufficiency.

Significance of Postoperative Systolic Murmur: Experience gained from mitral valvulotomy has indicated also that an apical systolic murmur not infrequently may appear postoperatively. When it is only of grade 1 or 2 intensity it probably does not represent significant mitral insufficiency and is compatible with a good functional result. When the murmur is of grade 3 intensity or louder and persists after several weeks, it has been considered evidence of a poor postoperative functional result, since mitral insufficiency probably has been produced. When a grade 3 or 4 systolic murmur appeared following valvulotomy, other signs of significant mitral insufficiency were almost universal and the functional result was generally poor. However, when the murmur was only of grade 1 or 2 intensity, it had little clinical significance. Not infrequently, a systolic apical murmur disappears following valvulotomy.

SYSTOLIC PULMONIC MURMUR

A systolic murmur of varying intensity and character is commonly heard and recorded in the pulmonic area in the presence of mitral stenosis (Fig. 13). The murmur may be blowing, harsh or rough in character and may vary in intensity from faint to loud. It is generally fairly well localized to the pulmonic area but may be propagated toward the apex and merge with the apical systolic murmur if one is present.

The systolic pulmonic murmur is associated with the dilatation and increased pressure in the pulmonary artery. The intensity of the murmur generally correlates well with the degree of dilatation of the pulmonary artery. Loud systolic pulmonic murmurs may occur especially with pulmonary hypertension.

Diastolic Murmur

Mitral stenosis may produce two types of diastolic murmurs which are of different character, location and significance. These are (1) a diastolic rumbling murmur in the mitral area due to the mitral stenosis and (2) a diastolic blowing murmur in the pulmonic area due to secondary pulmonary insufficiency (Graham Steell murmur). The apical diastolic murmur may have two components, a mid-diastolic rumble and a presystolic (atriosystolic) murmur.

APICAL DIASTOLIC MURMUR

The most characteristic and most diagnostic auscultatory finding of mitral stenosis is the rumbling apical diastolic murmur. With rare exception its presence indicates a significant degree of mitral valve narrowing. The character, duration and position in the cardiac cycle of the diastolic murmur may vary greatly in different stages of mitral stenosis. A change in the cardiac rhythm from sinus rhythm to atrial fibrillation will also alter the character of the murmur.

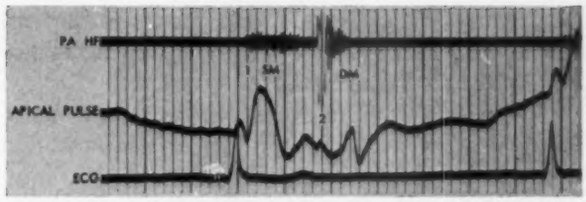

Fig. 13. *Pulmonary hypertension in mitral stenosis.* There is an early and mid-systolic murmur, a loud second pulmonary sound and an early decrescendo diastolic murmur (Graham Steell).

Auscultatory and Phonocardiographic Characteristics: The apical diastolic murmur is generally low-pitched and rumbling in character and in the phonocardiogram consists predominantly of low frequency vibrations[27,50] (Figs. 3 and 7). Occasionally, however, it is blowing or musical in quality and contains a larger high frequency component. A musical quality may be observed especially in the presence of a calcified mitral valve.

In the early stage of mitral stenosis the rumble may be confined either to the mid-phase of diastole following the opening mitral snap, or it may be entirely presystolic in type, occurring as a consequence of atrial systole and preceding and merging with the first sound (atriosystolic murmur) (Fig. 10). As the mitral stenosis progresses the murmur becomes of longer duration and occupies the greater part of diastole, but becoming accentuated in presystole (Figs. 1, 2, 3 and 11).

The diastolic murmur of mitral stenosis is generally best heard in the apical or mitral area. It often is transmitted to the left axillary region and sometimes medially toward the lower left sternal margin. Occasionally, it even may be transmitted upward toward the pulmonic area, just like the opening snap.[17] In many cases, however, the murmur may be localized to a small area in the apical or left axillary region no larger than the size of the chest piece of the stethoscope or recording microphone, and may easily be missed unless the mitral area is explored carefully. The murmur is more evident when the patient is in

the recumbent position rather than sitting up, and it may easily be missed by casual examination in the sitting or standing position.

Since the murmur is low-pitched and rumbling in quality it is heard better with the bell type of chest piece rather than the diaphragm, since the latter may not transmit low-pitched vibrations. Similarly, in recording the murmur a microphone which amplifies the low-pitched vibrations is preferable to one which excludes them (Fig. 5). During auscultation as well as recording, the chest piece or microphone should be applied lightly to the chest wall to avoid filtering out the low frequency sounds. Two other procedures are helpful in eliciting the presence of the diastolic murmur of mitral stenosis. These are exercise to increase the patient's heart rate and auscultation in the left lateral recumbent position.

Palpable Thrill: When the diastolic murmur is sufficiently loud it produces a palpable diastolic thrill in the mitral area. This may be visible in the recorded tracing of the apex beat as a series of course vibrations following the impact of the opening mitral snap. Generally, the occurrence of a diastolic thrill depends upon the intensity of the diastolic murmur.

Relation of Murmur to Second Sound and Opening Snap: Since the apical diastolic murmur is produced by the narrowing of the mitral valve, which impedes blood flow into the left ventricle, it is evident that the onset of the murmur cannot occur until after the mitral valve has opened. As has been shown previously, the opening of the mitral valve is marked by the audible opening snap or mitral click which may follow the second sound by an appreciable period, ranging from 0.03 to 0.14 second.[37] Therefore, the apical diastolic murmur usually does not begin immediately after the second sound. Furthermore, not infrequently there is a free interval between the opening snap and the onset of the diastolic rumble, so that the murmur is mid-diastolic rather than early diastolic in time (Fig. 2). This helps to differentiate it from the diastolic murmur of aortic or pulmonic insufficiency which may be transmitted down from the base to the mitral area and which generally starts immediately after the second sound.

Atriosystolic Murmur: In the presence of normal sinus rhythm, the diastolic rumble of mitral stenosis is accentuated either at its onset in early diastole (Fig. 2) and/or at its termination in late diastole or presystole (Figs. 1, 2 and 7). The initial components of the murmur occur during the phase of rapid ventricular filling when the velocity of blood flow through the mitral valve is generally the greatest. This produces the early accentuation of the murmur immediately after the opening mitral snap. The presystolic accentuation occurs as a consequence of left atrial contraction which produces an additional acceleration of A-V blood flow. Also, the vibrations produced by atrial contraction (auricular sound) are superimposed upon the diastolic murmur. These factors produce a reinforcement of the murmur in late diastole and a typical crescendo quality. On the other hand, the presystolic accentuation of the murmur frequently may be more apparent than real.[51] The murmur appears to be accentuated in presystolic because it terminates in a snapping and loud first sound.

Variations in Duration of Diastolic Murmur: It is evident that the duration of the diastolic murmur and its position in the cardiac cycle may vary considerably from case to case. It may be short, late in the diastolic phase and crescendo in quality in some cases. In others it may be early in the cycle and follow the opening snap. As the lesion progresses, the entire diastolic period from the opening snap to the first sound may be completely filled with a murmur (Figs. 1, 2, 3, 7 and 11). Not infrequently there appear to be two components, one in early and one in late diastole, with a comparatively silent gap between them. Occasionally, the murmur may begin in early diastole and have a decrescendo quality. This is particularly common in auricular fibrillation when the ventricular rate is slow and the diastolic intervals long.

A prolonged diastolic murmur may fill the entire diastole from the opening snap to the first sound and may show no presystolic accentuation, even in the presence of normal sinus rhythm. This may be explained in the following way. At the end of diastole when the atria are about to contract, the ventricles are already so full and the mitral leaflets have already floated to such a high level that the final contraction of the atria does not produce sufficient movement of the valve leaflets or additional turbulence of the blood stream to produce audible intensification of the murmur.

Effect of Atrial Fibrillation: The appearance of atrial fibrillation or other cardiac arrhythmias in the course of mitral stenosis may alter pro-

foundly the character of the diastolic murmur. If the ventricular rate is rapid and the diastolic intervals shortened, it may be impossible to detect any diastolic murmur until the ventricular rate is slowed by therapy. Since the atria no longer contract in atrial fibrillation, the presystolic accentuation of the murmur disappears (Fig. 4). However, the accentuated first sound and the opening snap are unaffected. When the ventricular rate is slowed excessively and the diastolic intervals become quite long, the diastolic murmur has a distinct decrescendo character. It begins early in diastole following the opening snap, occupies mid-diastole and then may disappear entirely before the next delayed cardiac cycle begins, leaving a silent interval prior to the next first sound (Fig. 5).

Not infrequently, the diastolic murmur of mitral stenosis is described as or appears to be crescendo in quality, even when atrial fibrillation is present. This, of course, is impossible and is the result of an error in auscultation or graphic interpretation. In atrial fibrillation there are short and long diastolic intervals; if the diastolic interval is short, the succeeding accentuated first sound may occur during or at the end of the diastolic rumble. The superposition of the first sound and the early or mid-diastolic murmur may produce a pseudopresystolic accentuation of the murmur. In the same case, however, when a longer diastolic interval occurs, it will be observed that there is no presystolic accentuation, for the first sound will occur after the diastolic murmur is terminated. Therefore, the characteristic murmur of mitral stenosis in the presence of atrial fibrillation is a mid-diastolic murmur, usually accompanied by an accentuated first sound and opening mitral snap.

Effect of Other Arrhythmias and Heart Failure: There are several other arrhythmias and clinical situations in which it may be difficult to detect a diastolic murmur of mitral stenosis, particularly when the murmur has been confined to late diastole or presystole.

(1) If atrial fibrillation and A-V block or nodal rhythm coexist, a presystolic murmur may disappear even in the presence of a regular heart rate.

(2) Similarly, during nodal rhythm or nodal tachycardia, a presystolic or atriosystolic murmur may disappear. In nodal rhythm the atria contract while the ventricles are in systole so that the mitral valve leaflets are never in the proper position to be snapped together by atrial contraction. Therefore, there is no presystolic murmur or late accentuation of a diastolic murmur. In the transition from nodal rhythm to sinus rhythm the very first sinus beat will produce a clear-cut presystolic murmur.

(3) In the presence of partial A-V heart block with a varying P-R interval, the presystolic murmur will vary in intensity and duration as the P-R interval lengthens and shortens.

(4) With atrial flutter the quality of the first sound and the presystolic murmur may vary depending upon the relationship of the previous atrial contraction to ventricular contraction. In flutter with a fixed block the first sound and diastolic murmur remain the same.

(5) In the presence of advanced congestive heart failure and atrial fibrillation, the cardiac chambers are dilated and contain large volumes of residual blood. The difference in A-V pressure (A-V gradient) is small, and insufficient motion and turbulence of the blood are present to produce an audible or recordable diastolic murmur. In such cases the diagnosis of mitral stenosis must be made by other methods.

Change in the Diastolic Murmur Following Valvulotomy: As a general rule, the diastolic murmur is diminished following successful operation and rarely disappears completely.[9,10,52,53] However, since the intensity of the diastolic murmur correlates poorly with valve size no conclusion as to the adequacy of the operation may be made on this basis. Of greater importance is a change in the length of the diastolic murmur. The presystolic murmur disappeared in 42 per cent of the patients in one series;[4] two-thirds of these patients had excellent results. When the presystolic murmur persisted after operation only one-third of the patients had good results. Not infrequently, there is no significant change in the auscultatory findings and yet the patient apparently has benefited greatly from the operation.

PULMONIC DIASTOLIC MURMUR (GRAHAM STEELL)

Effect of Pulmonary Hypertension on Heart Sounds: Before describing the Graham Steell murmur special comment should be made on the effect of pulmonary hypertension on the auscultatory findings in mitral stenosis. Several atypical features have already been mentioned in the individual sections. However, they will be repeated briefly because special emphasis should be placed on the patients with pulmonary hypertension since they comprise up to 10 per cent of patients with mitral stenosis and often show atypical features.[42]

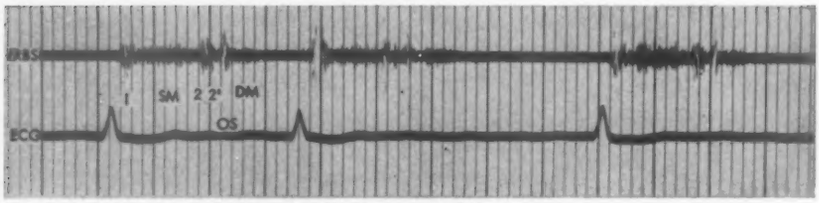

FIG. 14. *Pulmonary hypertension and atrial fibrillation.* There is narrow splitting of the second sound in the first cycle but in the subsequent cycle the second sound is single. The opening snap is well transmitted to the pulmonary and Erb's area. There is a systolic murmur and early diastolic high frequency murmur due to the pulmonary hypertension.

In about half of such patients, the first sound will be normal or only slightly accentuated.[42] The mitral diastolic and presystolic murmur may disappear;[40] it was reported to be absent in 50 per cent of the cases in one small series.[42] The pulmonary second sound invariably increases in intensity and an early diminuendo diastolic murmur (Graham Steell) signifying pulmonary incompetence is common. Excluding patients with dominant mitral insufficiency, it is in these patients that an opening snap is often absent. The signs of tricuspid incompetence are common. In fact, when tricuspid incompetence is present it is highly probable that the pulmonary vascular resistance is high, although this rule does not necessarily hold true when there is atrial fibrillation.

Pulmonary Diastolic Murmur: The Graham Steell murmur of pulmonary incompetence is an early diastolic murmur which is soft and blowing in character[44,54] (Figs. 13 and 14). It is generally loudest in the pulmonic area and transmitted down along the left sternal margin toward the apex, and therefore, may be fairly prominent at Erb's point. Its intensity is usually only grade 1 or 2 but sometimes it may be grade 3 and harsh and musical in quality.

Unlike the apical diastolic murmur of mitral stenosis, which may be transmitted upward toward the pulmonic area, the Graham Steell murmur is loudest in early diastole and begins with or merges with the end of the second sound. Therefore there is no silent interval between the second sound and the murmur. In the phonocardiogram the murmur is composed of high frequency components, which begin with the end of the second sound and fade out in early or mid-diastole.

Differentiation from Aortic Insufficiency: A most difficult differential diagnosis is that between the Graham Steell murmur and the diastolic murmur of aortic insufficiency. The character, intensity and location of the two murmurs may be similar and differentiation may be impossible. The direction of transmission down the left sternal margin toward Erb's point is often the same for both murmurs. Of course, the presence of findings in the electrocardiogram and roentgenogram indicating left ventricular enlargement would suggest aortic insufficiency, but the absence of such findings does not necessarily exclude the presence of aortic insufficiency. On the other hand, the presence of pulmonary hypertension or a markedly dilated or actively pulsating pulmonary artery is suggestive evidence of pulmonic insufficiency.

The differential diagnosis between the murmurs of pulmonic and aortic insufficiency associated with mitral stenosis has attained increased importance in recent years since the advent of mitral valve surgery. The proper interpretation of a diastolic murmur at the base and left sternal margin is important in arriving at a decision for or against mitral vavulotomy, since the presence of aortic insufficiency may be a relative or absolute contraindication for surgery, depending on its severity and the presence or absence of left ventricular enlargement. Often, such differentiation cannot be made preoperatively but only after valvulotomy has been performed. If the murmur becomes less intense or disappears, it indicates that it was probably a Graham Steell murmur. If it becomes louder it suggests the presence of aortic insufficiency.

Graham Steell Murmur Following Valvulotomy: Our knowledge concerning the frequency of the Graham Steell murmur in mitral stenosis has increased since the introduction of mitral valvulotomy. Since well documented information concerning this murmur is so meager it may be profitable to summarize the recently reported cases. The average of several series indicates that approximately 13 per cent of patients with mitral stenosis have a Graham Steell murmur.[4,52,53,56] At operation the pulmonary artery was markedly dilated. Its presence was

generally associated with a marked increase in the pulmonary vascular resistance. It was never present when the pulmonary vascular resistance and pulmonary artery pressure were normal or only slightly elevated.

Calcification of the Mitral Valve

With the advent of mitral valve surgery it has become of considerable practical importance to be able to detect the presence of calcification of the mitral valve. Calcification of the mitral valve generally is associated with a severe degree of stenosis or predominent insufficiency and may make successful commissurotomy more difficult, or be a contraindication to surgery. Its presence may require the use of the knife rather than digital fracture of the leaflets and may increase the hazards of the operation, such as arterial embolization. Careful auscultation of the heart and phonocardiography may aid in the diagnosis of mitral calcification, although the findings are not as important as direct visualization of the calcification by fluoroscopy or radiography, preferably the former.

The various modifications of the auscultatory and phonocardiographic findings of mitral stenosis when calcification is present have been summarized.[40] When the mitral valve leaflets, chordae tendinae or annulus fibrosus are involved, the cusps may become inflexible and too rigid to move. This may result in muffling of the snapping accentuated first sound, appearance of a systolic murmur due to mitral insufficiency, disappearance of the mitral opening snap and occasionally, a change in character of the diastolic murmur from low-pitched and rumbling to high-pitched and musical in quality.

First Sound: The rigidity of the calcified valve leaflets results not only in muffling of the accentuated first sound, but also in lowering of pitch as well as of intensity (Fig. 10). It is less easily palpable since its vibrations are not well transmitted to the chest wall. Not infrequently the first sound may be obscured by the accompanying prominent early systolic murmur. On the other hand, a loud snapping first sound may persist even with marked calcification or may be brought out by exercise or during tachycardia.

Systolic Apical Murmur: The presence of calcareus nodules on the valve cusps and rigidity of the leaflets would be expected to produce a systolic murmur due to mitral insufficiency. Actually, the incidence of an apical systolic murmur is doubled as compared with control subjects with mitral stenosis and no calcification. The loudness of the murmur is generally increased and murmurs of grade 3 intensity or louder are not uncommon.

On the other hand, gross calcification may be present in the absence of any systolic murmur or detectable mitral regurgitation. In one series, one-fifth of the patients with gross valvular calcification had no audible systolic murmur; at operation six of twelve patients had no palpable regurgitant jet.[40] Nevertheless, the incidence of mitral regurgitation, as determined by the presence of a regurgitant jet and by other clinical signs of mitral insufficiency (loud systolic murmur, left ventricular enlargement), was twice as high as in the group with mitral stenosis and no calcification, being present in one-half of the patients.

The absence of significant mitral regurgitation in half the patients with gross mitral calcification may be difficult to explain. In some it may be attributed to the localization of the calcification mainly to the annulus fibrosus or floor of the atrium leaving the valve leaflets and chordae tendinae free and flexible. It is in such cases that the accentuated first sound and opening snap persist. However, when the valve cusps and chordae tendinae are grossly calcified, it is more difficult to explain how valve closure occurs without detectable regurgitation.

Mitral Opening Snap: Since the opening snap or mitral click is presumably produced by the opening movements of the mitral valve, it would be expected that increased rigidity of the valve associated with gross calcification would result in disappearance of the opening snap. Actually, it has been found that its incidence is cut almost in half and it is audible or recorded in less than one-half the cases. It has been observed, also, that the opening snap loses its characteristic sharp clicking quality. The frequent association of mitral insufficiency and calcification of the valves is another factor which results in disappearance of the opening snap. The persistence of the opening snap in almost half the cases, however, suggests that some flexibility of part of the valve cusps or chordae tendinae may persist and that there may be no significant regurgitation even in the presence of gross calcification.

Mitral Diastolic Murmur: In general, no detectable change in the intensity, pitch and quality of the diastolic murmur is observed in patients with mitral calcification. In an occa-

sional case, however, the murmur becomes softer, muscial and high-pitched in quality.

Conditions Simulating Mitral Stenosis

CONDITIONS SIMULATING THE PRESYSTOLIC MURMUR

Left Atrial Myxoma: There are several conditions which may simulate a presystolic murmur of mitral stenosis and lead to an erroneous diagnosis.[26,57–60] Only the most important of these will be dealt with. Obstructive lesions of the mitral valve such as a ball valve thrombus and a left atrial myxoma may not only cause a presystolic murmur, but all the classic findings of mitral stenosis including the opening snap may also be present.[61]

The majority of cases of atrial myxoma are discovered at the time of operation for suspected mitral stenosis but occasionally the diagnosis can be suspected preoperatively and confirmed by angiocardiography. A possibly differential point is a change in the character of the murmur with the subject in the supine and sitting position. Patients with myxomas have been described in whom a diastolic and presystolic murmur became systolic upon change from a supine to sitting position.[62] In addition, conditions for hearing the murmur of mitral stenosis are more favorable with the patient in the supine position, whereas with myxomas the sitting position apparently is best.[63] Because obstruction may be intermittent a diastolic murmur may also be only intermittently present; this may provide another clue for the diagnosis of a myxoma. This is, however, inconstant. In two cases of left atrial tumor seen by us these findings were not observed.

Accentuated Atrial Sound or Split First Sound: The presystolic murmur must also be differentiated from an atrial sound (presystolic gallop), split first heart sound and the Austin Flint murmur.[59,60] Wide splitting of the first sound occurs only with complete right bundle branch block. When this electrocardiographic pattern is present one must be exceedingly careful in diagnosing mitral stenosis on the basis of a presystolic sound itself. In such instances a mid-diastolic murmur and/or opening snap should also be present.

The presystolic (atrial) gallop may also be mistaken for a presystolic murmur. It may merge with the first sound and give the illusion of a presystolic crescendo. Atrial sounds are rarely heard in normal subjects but are not uncommon in patients with hypertensive heart disease. The differential diagnosis is further complicated by the occasional occurrence of a loud or delayed first heart sound in patients with hypertension although it never attains the sharpness or intensity observed in mitral stenosis. A mid-diastolic murmur and opening snap are never observed in patients with hypertensive heart disease.

Austin Flint Murmur: The Austin Flint murmur poses the greatest difficulty in the differentiation of presystolic murmurs simulating mitral stenosis. Although Flint[64] clearly described it as a presystolic blubbering murmur, many cardiologists consider any mid-diastolic or presystolic apical murmur caused by aortic regurgitation as examples of the Austin Flint murmur. A loud ejection sound in aortic regurgitation may be mistaken for the accentuated first sound and the frequent occurrence of a third heart sound (gallop) may be mistaken for an opening snap. In addition, the opening snap of mitral stenosis is delayed and occasionally absent with concommitant aortic regurgitation.[65]

In a subject with aortic regurgitation and a presystolic murmur it may be difficult to determine if associated mitral stenosis is present. When such a situation arises the phonocardiogram is of distinct aid to the clinician. It may document the presence of an opening snap. A loud and delayed first sound is further evidence for mitral stenosis but is occasionally observed in aortic regurgitation. The presence of atrial fibrillation favors mitral stenosis but is also observed in advanced aortic regurgitation. Conversely, a regular sinus rhythm, a soft first heart sound and a protodiastolic gallop favor aortic regurgitation as the cause for a mid-diastolic or presystolic murmur.

Intracardiac phonocardiography with the microphone in the left atrium in cases of mitral stenosis shows a mid-diastolic or presystolic murmur.[66,67] In one case of aortic regurgitation the left atrium phonocardiogram failed to demonstrate a presystolic murmur whereas the left ventricular phonocardiogram documented the presystolic murmur which is caused by eddies from the regurgitant blood.[67]

MID-DIASTOLIC MURMURS SIMULATING MITRAL STENOSIS

A mid-diastolic murmur not caused by structural narrowing of the mitral valve has been described in a number of different conditions which may be mistaken for mitral stenosis.

It was first described by Carey Coombs in 1924.[68] The quality (low-pitched and rumbling) is identical with that observed in mitral stenosis, but it never follows an opening snap but rather a third heart sound. It was first described as a sign of acute mitral valvulitis. Carey Coombs correctly pointed out that this is not evidence for mitral stenosis, because this murmur disappears after the acute stage of rheumatic carditis. He attributed it to edema of the valves.

Similar murmurs have been observed in any condition which increases blood flow across the mitral or tricuspid orifice such as ventricular septal defect, atrial septal defect, patent ductus arteriosus and mitral regurgitation. It has also been observed in instances of high output failure such as anemia. The clinical picture is such that confusion of those conditions with mitral stenosis is unusual but does occur.

The importance of recognizing that this murmur is functional and does not signify mitral stenosis cannot be overemphasized. The most reliable differentiating points are (1) its brief duration, (2) it begins with a third heart sound and never is associated with an opening snap, and (3) a presystolic murmur and accentuated first heart sound are not usually present.

Summary

The auscultatory and phonocardiographic characteristics of mitral stenosis are reviewed. This includes our experience with over 150 patients with mitral stenosis with minimal or no regurgitation proved at operation. The following features are considered to be characteristic of mitral stenosis:

1. The mitral component of the first heart sound is accentuated and delayed and gives rise to a palpable shock over the apex and precordium. With atrial fibrillation the intensity of the mitral component may or may not vary inversely with the length of the preceding diastole.

2. The second sound at the pulmonary area is normal or accentuated. Splitting of the second sound is not a conspicuous finding and is usually normal.

3. An opening snap is invariably present. It is maximal inside the apex and may be transmitted over the entire precordium.

4. A third heart sound is never audible but rarely may be recorded on the phonocardiogram.

5. A pulmonary ejection sound occasionally is audible but more commonly is recorded on the phonocardiogram. It signifies dilatation of the pulmonary artery and hypertension in the pulmonary circulation.

6. The diastolic murmur is low-pitched and rumbling in quality. It starts with or shortly after the opening snap and may continue through the entire diastolic phase or end before the first sound. In patients with sinus rhythm a presystolic (atriosystolic) murmur was invariably present.

7. A pulmonary diastolic decrescendo murmur which commenced with the pulmonary second sound was much more commonly audible than was recorded on the phonocardiogram.

8. A pansystolic apical murmur was rare and always less than grade 2 in intensity.

Marked pulmonary hypertension caused the greatest change in the findings described herein. These included a normal or only slightly accentuated first heart sound, an absent opening snap or a faint or even absent diastolic murmur. Calcification of the mitral valve also modified the auscultatory findings, producing muffling of the first heart sound, a frequent systolic murmur and disappearance of the opening mitral snap.

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The Auscultatory and Phonocardiographic Findings in Mitral Regurgitation*

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RECENT advances in open heart surgery have enabled the surgeon to attack the mitral valve directly in cases of regurgitation. Recognition of mitral regurgitation is important not only to determine which patients should undergo valvulotomy, but also to decide which patients should be operated on by the open heart technic.

Elaborate methods have been employed to evaluate patients with combined mitral lesions in order to determine the predominance of either stenosis or insufficiency. Left ventricular,[1] left atrial,[2] pulmonary artery and pulmonary wedge pressure pulses,[3,4] systemic arterial pressure pulses,[5] indicator dilution curves[6,7] and left ventriculography[8] have been studied extensively. Most of these procedures require left heart catheterization and are associated with some morbidity and on occasion even death. Unfortunately, despite the information obtained, a uniform separation of patients is not possible and at operation the surgeon may be surprised to find the clinical diagnosis is incorrect.[9]

Careful clinical auscultation and phonocardiography are still valuable methods for differentiating dominant stenosis from insufficiency.[10] They should not be neglected even in patients subjected to the diagnostic procedures just mentioned. Experience gained from these methods in patients subjected to mitral surgery in the past decade has enabled the clinician to predict with a high degree of accuracy the dominant lesion affecting the mitral valve.

This report deals with the findings in pure mitral regurgitation. The auscultatory characteristics of mitral stenosis have recently been reviewed.[11,12] The findings in combined lesions will be the subject of a subsequent report.[13]

ETIOLOGY

Not all forms of mitral regurgitation are amenable to surgical correction. Congenital (usually associated with an ostium primum defect) and rheumatic mitral regurgitation are two forms that are presently correctible. Regurgitation also may be secondary to a ruptured papillary muscle as a result of trauma or myocardial infarction, to calcification of the annulus fibrosus or to healed bacterial endocarditis. To date these forms have not been amenable to surgery, so that it is important to recognize all etiologies.

FIRST HEART SOUND

The first sound is normal in mitral regurgitation or more commonly diminished in intensity at the apex; it is rarely loud[5,14] (Fig. 1). Ordinarily, involvement of the mitral valve is more severe with regurgitation than with stenosis. This accounts for the inability of the valve cusps to be tensed suddenly, therefore, the first heart sound is decreased, dull and often inaudible. However, there are exceptions to this (Fig. 2). Venner[15] described three patients and Douglas[16] one patient with almost pure mitral regurgitation, proved at operation, associated with a loud first sound. These patients had supple, pliable valves without significant calcification. An opening snap was not audible in any of them.

The tricuspid component is generally soft at the apex and may be drowned out by the systolic murmur. Splitting of the first sound is not a feature nor is a delayed first sound a phonocardiographic observation. Some variability of the intensity of the first sound occurs with atrial fibrillation, a louder sound following the

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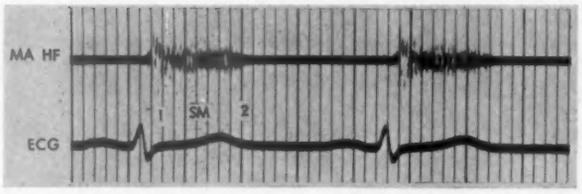

FIG. 1. *Mitral regurgitation.* High frequency apex phonocardiogram demonstrating a normal first sound and a holosystolic murmur extending up to and embracing the second sound. Symbols for this and subsequent illustrations: 1 = first heart sound; 2 = second heart sound; 3 = third heart sound; OS = opening snap; SM = systolic murmur; DM = diastolic murmur; A = aortic valve sound; P = pulmonary valve sound; MA = Mitral area (apex); HF = high frequency recording; LF = low frequency recording; Jug = jugular venous pulse; Car = carotid artery pulse; Liver = liver pulse.

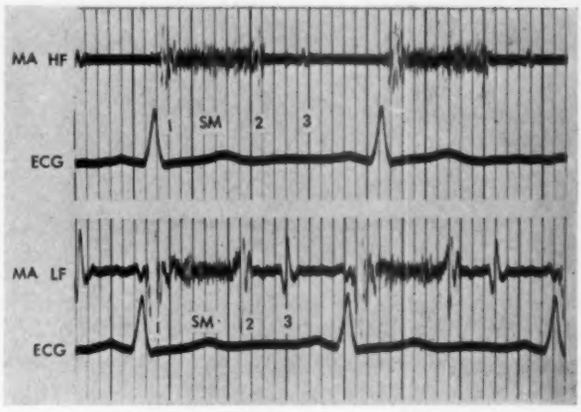

FIG. 2. *Mitral insufficiency with a loud first heart sound.* The lower tracing (low frequency) shows a high amplitude first heart sound in this patient who had pure mitral insufficiency. In addition there is a loud third heart sound also best demonstrated in the low frequency recording.

short diastolic periods. There is no correlation between the loudness of the first sound and the severity of the regurgitation.

SECOND HEART SOUND

In the normal subject on inspiration there may be splitting of the second heart sound up to 0.08 second due to an increased right ventricular stroke volume, prolonging ejection and delaying pulmonic valve closure. On expiration, however, the splitting narrows, and the sound normally becomes single. Fixed splitting of the second sound is abnormal and occurs with right bundle branch block and atrial septal defect.[17] Paradoxical splitting of the second sound (reversal of the normal relationship between closure of the aortic and pulmonary valves) occurs in some cases of aortic stenosis, left bundle branch block, patent ductus arteriosus and rarely systemic hypertension.

Since useful clinical information can be obtained by carefully noting the character of the second sound, auscultation in the pulmonary area for the degree of splitting should be done carefully. Closure of the pulmonary valve is rarely heard at the apex unless hypertension is present in the lesser circulation which increases its intensity. In mitral regurgitation,

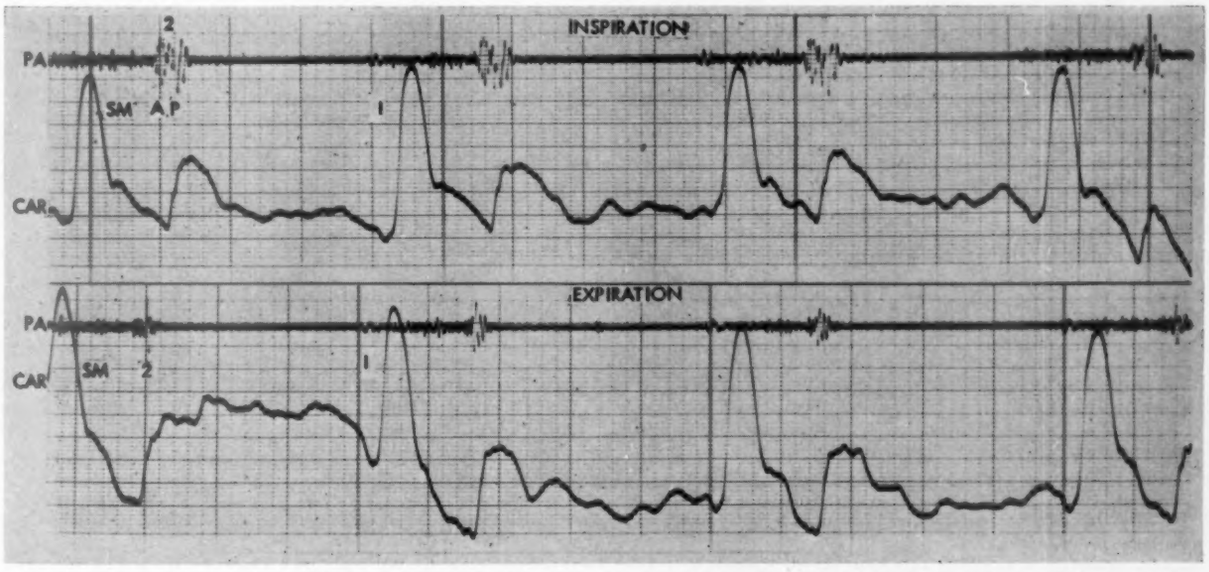

FIG. 3. *Effect of respiration on splitting of the second heart sound.* On inspiration (*above*) there is splitting of the two components of the second sound. The pulmonary closure follows the aortic by 0.05 second. On expiration (*below*) the two components become single as in normal subjects. The systolic murmur is poorly transmitted to the pulmonary area and is of low intensity, but it remains holosystolic.

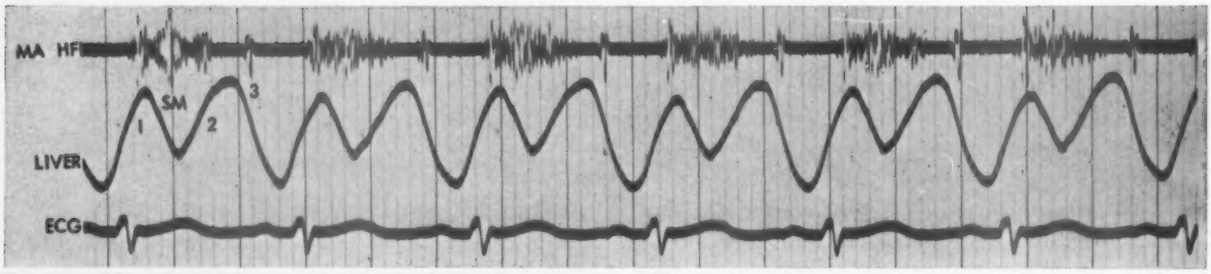

FIG. 4. *Mitral insufficiency with subacute bacterial endocarditis.* There is a holosystolic murmur and a prominent third heart sound. The first heart sound is of normal intensity.

there are two features of the second heart sound that require discussion: intensity and splitting.

Intensity: Since pulmonary hypertension is uncommon in pure mitral regurgitation, an accentuated second pulmonary sound would be unexpected. This is confirmed by auscultation and phonocardiograms. When identified, the pulmonary sound is normal in the majority of cases[14] (Fig. 3). With associated mitral stenosis or with left heart failure, however, the pulmonary component may become accentuated.

Splitting: It has been observed that wide splitting of the second sound is common in mitral regurgitation.[14,17] The explanation given is that since there are two portals for escape of blood from the left ventricle the ejection period is shortened and, therefore, splitting is due to early closure of the aortic valve rather than a delayed closure of the pulmonary valve. Furthermore, in mitral regurgitation, although splitting widens on inspiration, on full expiration the splitting narrows but does not usually become single as in the normal (Fig. 3). With right ventricular failure, the split remains more or less fixed and abnormal because the right ventricle cannot increase or decrease its stroke volume. In such instances the splitting may be up to 0.10 second.[17]

THIRD HEART SOUND

A third heart sound at the apex can be heard in the majority of patients with mitral regurgitation[18] (Figs. 2 and 4). This is caused by the increased flow across the mitral valve which is necessary to compensate for the amount which regurgitates into the left atrium. Although low-pitched, this sound may attain a remarkable intensity. It occurs from 0.12 to 0.24 second after closure of the aortic valve. Generally, it is fairly well restricted to the apical area and best heard in the supine position on full expiration. Occasionally, it can be audible at Erb's area.

The accentuated third sound must be differentiated from an opening mitral snap and a split second sound. Clinically, its localization to the apical area is the best differential point. An opening snap is usually best heard inside the apex, but is widely transmitted and well heard at the pulmonary and even aortic areas. In addition, the opening snap is sharper and occurs closer to the second sound, the interval averaging 0.07 second after closure of the aortic valve. However, there may be some overlap in timing of the opening snap and third heart sound.

A split second sound is differentiated by its localization to the pulmonary area and its narrowing on expiration. In the phonocardio-

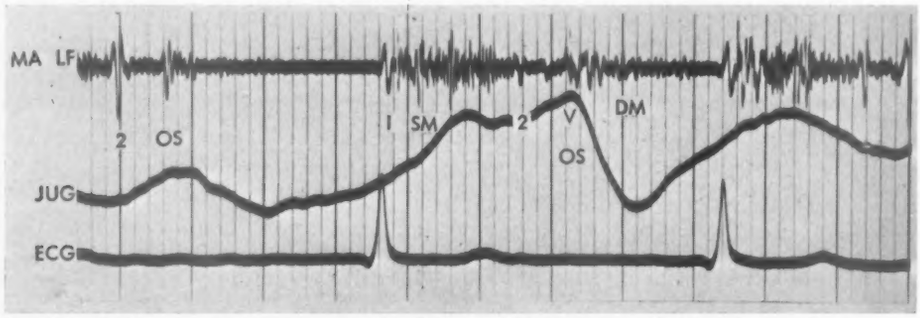

FIG. 5. *Combined mitral stenosis and insufficiency.* There is an additional sound occurring 0.13 second after the second sound which could represent either an opening snap or third heart sound. In this case the jugular venous pulse tracing shows the extra sound occurs at the peak of the V wave, indicating that it is an opening snap. There is a holosystolic murmur and a mid-diastolic murmur with a normal first heart sound.

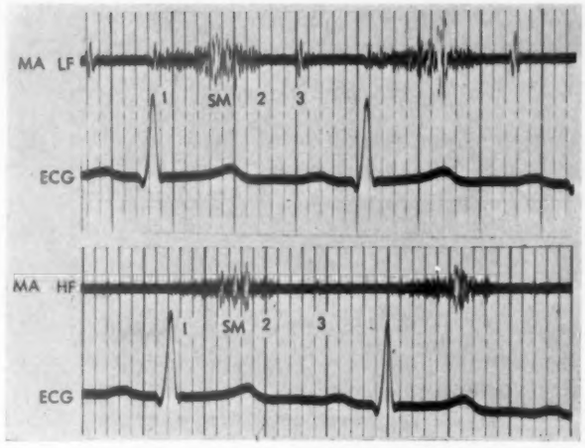

FIG. 6. *Mitral regurgitation.* The first heart sound is diminished in intensity. There is a holosystolic murmur rising to a crescendo in late systole and extending to the second sound at the apex. A prominent third sound is present.

gram with a simultaneously recorded venous pulse, the third sound appears during the descent of the V wave. An opening snap occurs at the peak of the V wave (Fig. 5) and a split second sound on its ascending limb.

An opening snap is never heard in pure mitral regurgitation. Its presence signifies some degree of stenosis although regurgitation may be the dominant lesion[5] (Fig. 5).

Systolic Murmur

The most important feature of the mitral systolic regurgitant murmur is its characteristic relationship to the first and second heart sounds. Since the left ventricular pressure exceeds left atrial pressure throughout systole, blood must regurgitate during this time. In fact, it continues even after closure of the aortic valve because left ventricular pressure is still higher than atrial pressure for a short time.[19] This

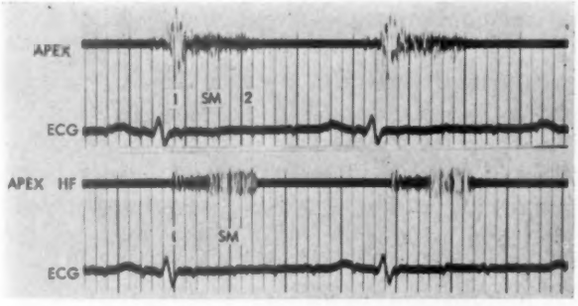

FIG. 7. *Mitral insufficiency with valve calcification.* The first sound is of normal intensity and is followed by a holosystolic murmur of high frequency which is accentuated in late systole and obscures the second heart sound at the apex.

explains the *pansystolic* character of the murmur and also the frequent absence of an audible second sound at the apex (Fig. 7). There may be mid- or late systolic accentuation or a plateau murmur (Figs. 1, 2, 4 and 6). Clinically the murmur may appear to be confined to late systole, but the phonocardiogram shows a pansystolic murmur, the earlier systolic vibrations being of low intensity and not audible[14] (Fig. 6).

Of distinctly less importance are the intensity, quality and distribution of the murmur. In fact, these may vary greatly and may be related to the etiology, presence or absence of congestive heart failure, and the degree of calcification of the valve or annulus.

The *intensity* of the murmur is usually described as loud (grade 3 or 4) and maximal at the apex. A thrill is occasionally present. The murmur fades out toward the base of the heart where it is rarely louder than grade 2 (on a scale of 6) (Fig. 3). An exception to this is regurgitation caused by rupture of a papillary muscle in which case a loud, harsh murmur and thrill may be present over the aortic area or carotid artery.[20–23] The degree or severity of the regurgitation cannot be assessed by the intensity of the murmur, but in general the loudest murmurs are more likely to be associated with severe regurgitation than not.

Maximal *radiation* occurs toward the axilla and left scapula, but in patients with giant left atria, the murmur may be well heard to the right of the sternum and over the right scapula.

The *quality* of the murmur may vary from being harsh, rough and course in the case of a ruptured chorda or papillary muscle to moderately harsh and blowing in rheumatic mitral insufficiency. More often, it is of medium harshness or blowing. With heavy calcification the murmur may be musical or harsh[24,25] (Fig. 7). In all instances, the murmur is high pitched.

Late *systolic clicks* have been observed in some cases.[14] These, of course, are not related to aortic ejection but may be caused by distention of the left atrium. More likely, they are extracardiac sounds due to the impact of the expanding atrium against surrounding structures.

Diastolic Murmurs

Two types of diastolic murmurs have been observed in mitral regurgitation. An *early diastolic murmur* inside the apex has been observed in some instances and is more often

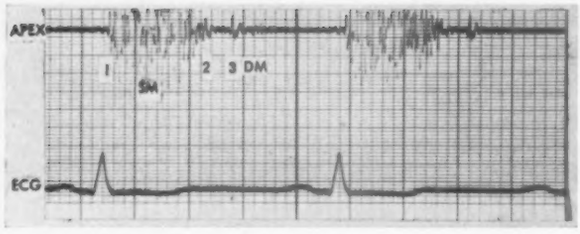

FIG. 8. *Mitral regurgitation.* There is a holosystolic murmur of great intensity, a third heart sound and a mid-diastolic low frequency (Carey Coombs) murmur.

recorded on the phonocardiogram than audible.[14] Although it is impossible to exclude insufficiency of the semilunar valve, several patients with this murmur, who subsequently underwent postmortem examination, showed no disease of the aortic or pulmonary valve. Wiggers and Feil[26] demonstrated that atrial and ventricular pressures may not become equalized until after closure of the semilunar valve, and consequently, regurgitation may continue into early diastole. Furthermore, electrokymographic studies show expansion of the left atrium continues for a short time after the second sound.[27]

A short *mid-diastolic apical murmur* following a third heart sound has been observed in mitral regurgitation and is caused by torrential blood flow rather than stenosis of the mitral valve (Fig. 8). It has been termed the Carey Coombs murmur and is observed in any condition leading to increased left ventricular filling.[19] The importance of this murmur, of course, is not to consider it as evidence for mitral stenosis. Although low-pitched and rumbling, it is always short, follows a third sound rather than an opening snap and is not associated with other signs of mitral stenosis such as a loud first sound or a presystolic murmur.

Intracardiac Phonocardiography

With the phono catheter in the left ventricle there is a systolic murmur and, in addition, there may be a short diastolic murmur which is probably a Carey Coombs filling murmur. Sounds recorded from the left atrium vary depending upon the distance of the catheter from the mitral valve. When near the valve a loud holosystolic murmur is always recorded.[28] The explanation for this is not clear. Intracardiac phonocardiography documents the origin of the murmur at the mitral valve, and in general merely confirms the impressions gained from careful auscultation and conventional phonocardiography; it is of no additional value in determining the state of the mitral valve.

Differential Diagnosis

Mitral regurgitation must be differentiated from the following conditions: (1) functional apical systolic murmur, (2) ventricular septal defect, (3) tricuspid regurgitation and (4) aortic stenosis. In some instances, it may be necessary to rely on other clinical data for a final decision. However, in most cases a differentiation may be made on the basis of auscultation and phonocardiography.

Functional murmurs only occasionally give difficulty. The first sound is normal and the second sound normally split. They are shorter, rarely pansystolic, and of a different quality, being softer more blowing and musical.[29,30] Occasionally, they are fairly harsh and have a late systolic crescendo which is commonly observed in mitral regurgitation. A normal cardiac size and electrocardiogram do not always exclude mitral regurgitation because early in the disease these may be within normal limits.

Ventricular septal defects cause pansystolic murmurs, third heart sounds and a Carey Coombs[31] murmur. These murmurs, however, are generally louder, maximal over the fourth left intercostal space, more commonly associated with a thrill and much louder over the base of the heart than in mitral regurgitation. The first sound is normal, and splitting of the second sound is variable, but an accentuated closure of the pulmonary valve is much more commonly observed (Fig. 9).

Tricuspid regurgitation may be difficult to differentiate from mitral regurgitation in patients with mitral stenosis. Schilder and Harvey[32] pointed out that not only may the tricuspid regurgitant murmur be identical to the mitral regurgitant murmur in timing and quality, but also with right ventricular enlargement in mitral stenosis the tricuspid valve may be rotated to the left so that the maximal intensity of the murmur is at the apex. Accentuation of the murmur on inspiration is a helpful sign, when present. Radiation is to the right of the sternum rather than to the axilla. Often, both lesions coexist which complicates matters even more.

Aortic stenosis causes an ejection murmur, and although it may be loudest at the apex it is still loud at the base and its timing characteristics are preserved. Thus, it begins after the

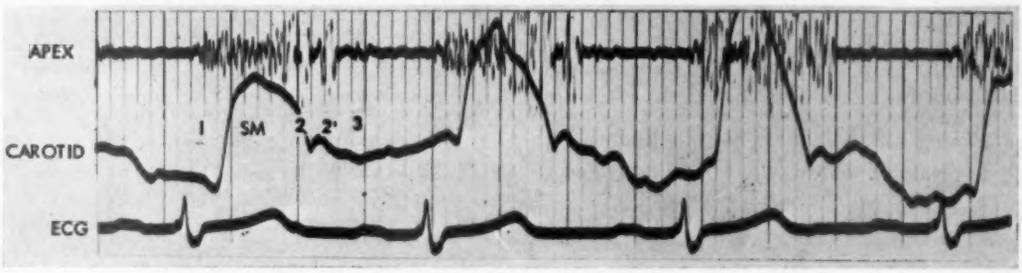

FIG. 9. *Ventricular septal defect.* Note the similarity to the murmur of mitral regurgitation. This patient had a large ventricular septal defect. There is a holosystolic murmur of great amplitude (intensity) and a third heart sound. The second sound is widely split and the pulmonary component is well heard and recorded at the apex, indicating an accentuated closure.

first sound, is often preceded by an ejection click and ends before a delayed and decreased second sound. The second sound is occasionally inaudible so that the murmur may appear to be pansystolic. However, the second aortic sound is usually identified in the phonocardiogram, proving the murmur to be ejection in type.

SUMMARY

The auscultatory and phonocardiographic findings in pure mitral regurgitation are reviewed. They may be summarized as follows:

1. The first sound is normal or decreased in intensity.
2. The second sound is commonly split due to early closure of the aortic valve, but marked accentuation of the pulmonic second sound is rarely observed.
3. An apical third sound is a frequent finding.
4. A mitral opening snap is never heard.
5. The systolic murmur is pansystolic. Late systolic accentuation of the murmur and a late systolic click occassionally are observed.
6. There may be an early diastolic murmur not caused by semilunar valve incompetence.
7. A short mid-diastolic rumble following a third sound (Carey Coombs murmur) may occur and does not signify mitral stenosis.

Differentiation of this lesion must be made from other conditions associated with a systolic murmur, including functional murmurs, ventricular septal defect, tricuspid regurgitation and aortic stenosis.

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Historical Milestones

Armand Trousseau on Acute Articular Rheumatism

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During the early decades of the nineteenth century French medicine reached high levels of influence. Many young American physicians were attracted to Paris, where they studied with Pierre Louis and his able contemporaries. Later in the century Germany and Austria became the magnet for physicians from the United States, while France never lost its appeal for Latin Americans. These considerations, plus the increasing inability of American physicians to cope with foreign languages, explain the fact that one rarely encounters an American who has read Armand Trousseau (1801–1867), while many of our visitors from Colombia and other countries to the south of us display familiarity with his writings. The loss is certainly to be deplored, since Trousseau's lectures are filled with instructive descriptions and comments, presented in a vivid manner which both entertains and enlightens.

The following text has been taken from Trousseau's "Lectures on Clinical Medicine Delivered at the Hôtel Dieu, Paris," translated by P. Victore Bazire and John R. Cormack, volume 4, pages 432 ff., London, 1868–1872, New Sydenham Society.

* * *

EXCERPTS FROM TROUSSEAU'S LECTURE ON ACUTE ARTICULAR RHEUMATISM AND ULCERATING ENDOCARDITIS

We have now been engaged in the study of gout and nodular rheumatism: and at the beginning of the year, I devoted several lectures to the clinical study of cerebral rheumatism. To-day I wish to discuss acute articular rheumatism, without intending, however, to give you a complete systematic description of the disease. Let me remark, that you will not see the disease at the bedside of the patient always presenting itself with the retinue of symptoms and complications described in works on pathology. At the close of the lecture, I shall call your attention to a newly described complication of articular rheumatism to which the name *ulcerative* endocarditis has been given. Let me here remark, however, that this modification of endocarditis may occur irrespective of any rheumatic manifestation.

Hardly a month passes during which you have not an opportunity of studying rheumatic arthritis in our clinical wards. The action of cold, particularly when the surface of the body is covered with sweat, is a very frequently determining cause in persons of the rheumatic diathesis. When you interrogate the patients at the hospital, nearly all of them will tell you that they have been struck with cold, either when hard at work or immediately after discontinuing severe labour. Some will say that they have been exposed to a draught of air, and that they have felt the whole body enveloped in cold. Others will tell you that they have been exposed to cold when passing from a hot to a cold damp atmosphere. In the evening, in the night, or during the next day, after experiencing these sensations, the patients are seized with shivering, succeeded by great heat and perspiration, and at the same time, nearly always, with acute fever and profuse sweating.

Rheumatic arthritis is continuous, hardly ever presenting paroxysms. The pulse is rapid, large, and resisting. The sweating is always profuse, and when the patients are uncovered, you can see the perspiration collected in little

drops over nearly the whole body. The perspiration has a peculiar odour, such as is hardly ever met with in other febrile diseases. You will also be struck with the paleness of the complexion: the face itself is often of a dull blue, and this general pallor is in strong contrast with the bright red hue of the skin.

There is loss of appetite. The tongue is white, but only slightly saburral: there is no tendency to vomit: constipation is the rule in such cases. The only complaint made by the patients is of pain in the joints. You will observe that they assume the dorsal decubitus, and remain motionless in bed, in dread lest the acute pain in the articulations be aroused by the slightest movement. The pain often first declares itself in the knees and insteps: afterwards, at the end of a period varying from some hours to three or four days, we find numerous joints invaded by the rheumatic inflammation. The pain has sometimes an upward progress: that is to say, that it ascends from the insteps to the knees and haunches, or from the wrists to the elbows and shoulders. It is not unusual for the disease to declare itself, in the first instance, only upon one side of the body, and subsequently to invade, in similar order, the joints of the other side...

In acute articular rheumatism, all the joints, large and small, may be attacked in succession. The articulations of the clavicle with the sternum and acromion, the maxillary articulations, and those of the vertebral column, may be seats of rheumatic pains.

Rheumatism, then, has a special predilection for the joints, but, in general, it is the large joints which are most commonly invaded. Gentlemen, I have frequently pointed out to you the characters of rheumatic arthritis. At the bed of the patient, we have seen that the affected joints were swollen and painful. The swelling is in the tissues which surround the joints; but this swelling is principally an intra-articular effusion. You cannot put your hand on the joint or cause the slightest movement of the articular surfaces without occasioning very severe pain. By applying the hand gently to the diseased joints, a very appreciably increased temperature can be detected. In a very few cases, redness may be remarked around the large joints, as is seen in arthritic affections of another kind. In rheumatism, there is a white swelling of the superficial tissues, but when the rheumatism is in the wrist, hand, instep, or small joints of the foot, the swelling has a rosy hue. In the course of the numerous tendinous sheaths of the wrist and instep, we see red streaks indicating the part which the sheaths have in rheumatic inflammation. In these cases, the wrist and hand are deformed. All the fingers are immovable, swollen, separated from one another, and have the shape of large spindles. The dorsal surface of the hand is rounded: there exists a state of true acute oedema, and between the hand and forearm, there is perfect continuity without any line of demarcation. Similar remarks are applicable to the foot, when it and the tibio-tarsal articulation are simultaneously invaded...

Gentlemen, you are acquainted with the important works of Mm. Bertin and Bouillaud upon rheumatic endocarditis and pericarditis. In his treatise on diseases of the heart, and also in his treatise on articular rheumatism, my learned colleague of the Faculty has set himself to demonstrate the law of coincidence of inflammation of the heart with articular rheumatism. According to the celebrated professor of La Charité, in acute, violent, generalised articular rheumatism, *it is the rule* to meet with coincident endocarditis, pericarditis, or endopericarditis. Gentlemen, there is no one more disposed than I am to render justice to the great labours of Professor Bouillaud, yet here I must state that an attentive study of the heart in a certain number of cases of acute articular rheumatism has not enabled me in all of them to discover symptoms of endocarditis, pericarditis, or endopericarditis. In fact, in several rheumatic patients who had acute fever with swollen and painful joints, I could not detect by percussion the dulness caused by effusion, nor by auscultation the friction sound of pericardial inflammation. A similar remark is applicable to the symptoms of endocarditis; for in a large number of cases of acute multiarticular rheumatism, I have not been able to hear a blowing sound at the apex of the heart: I have more frequently heard a blowing sound at the base, but it was a soft sound, and it extended into the vessels of the neck with the same softness; from which circumstance, and the fact that rheumatic patients are all very anaemic, I am inclinded to connect this blowing sound with anaemia. I think then, that the law, as laid down by Bouillaud, in relation to the coincidence of acute cardiac lesions with rheumatism is not so absolute, as he has assumed; but while I say this, let me add, that in a great many cases, I have been fortunate enough to be able to verify

fully the truth of the law of coincidence so well established by him.

Be that as it may, Gentlemen, you ought always most carefully to search for the cardiac symptoms which characterise acute lesions of the heart in articular rheumatism; and often, I repeat, you will have an opportunity to confirm by your own observation the law of coincidence laid down by Bouillaud. Recollect, however, that this coincidence may be wanting in acute polyarthritic rheumatism...

These remarks, however, Gentlemen, must be made under reserve, and whatever confirmation they may one day receive from your own observation, do not forget that rheumatism often attacks the heart, and is often the primary cause of the organic lesions to which the complex term of "aneurism of the heart" was formerly applied, and the varieties of which we now describe under the names of contraction and insufficiency of the cardiac orifices.

Valvular lesions of the heart have often assuredly for their primary cause an attack of acute articular rheumatism: clinical observation, however, will teach you that lesions of the mitral and aortic orifices may likewise exist without there being a possibility of discovering in the antecedents of the patients any articular manifestations of the rheumatic diathesis. While it is true that rheumatism often causes diseases of the heart, it must also be admitted that there are cardiac lesions originating in wholly different causes. To mention only one of them, alcoholic intoxication, which determines most remarkable alterations of nutrition in the fibro-serous coverings of the liver and brain, has certainly its part in the etiology of organic affections of the heart. This etiology is, moreover proved by the co-existence, so frequent in alcoholic drunkards, of lesions of the heart and cirrhosis of the liver...

When rheumatic inflammation attacks the heart, modifications of the functions of nutrition become apparent. The capillary vessels which ramify in the cellular tissue become more numerous: the plasma which they allow to transude through their walls no longer supplies normal epithelial cells, and the cellular tissue becomes infiltrated with new products, and with fat. The serous surface loses its natural smoothness, the membrane itself becomes thickened, and deposits new products on its surface—false membranes—which assume various forms, and may present all the characters of new membranes. The membrane which lines the cavity of the heart is, like the pericardium composed of two layers, a serous and a fibrous: in it, rheumatic inflammation determines lesions analogous to those which it produces in the pericardium. However, the modifications of nutrition caused by rheumatism are most remarkable on the folds of endocardium which constitute the mitral and aortic valves. Not only does the serous surface of these valves lose its smoothness, but it also often becomes the seat of fibrinous deposits, and of conjunctive cells resembling mulberry shaped granulations, either scattered or collected in groups. At other times, the thickened valves become the seat of calcareous deposits. These deposits, as has been shown by chemical analysis, are composed of carbonates of lime and soda...

When the joints have been the seat of rheumatic inflammation, they may, after a period of variable duration, recover their functional integrity; but there is no similar recovery after endocarditis: the lesions, be they ever so slight, are irremediable, and usually they become worse and worse. It is necessary, however, to remark that this evil progress may be very slow, leading neither necessarily nor immediately to great disorder of the cardiac function. The thickened valves may retain sufficient flexibility to continue to act as perfect valves, rising and falling regularly in such a way as to afford free passage to the blood and prevent its regurgitation into the cavities of the heart.

Though there be no functional lesion, and though the valves be but slightly thickened, and have lost little of their normal smoothness, an attentive ear can detect blowing sounds, which do not exist when the valvular apparatus is in a state of integrity.

The structural modifications of the valves may remain very slight for many years: at other times, the nutrition of the valves has been so much modified by the rheumatism that the lesion goes on constantly increasing, presenting to the ear rough and rasping blowing sounds. The circulatory function may, nevertheless, not appear seriously impaired, from, simultaneously with the contraction of the cardiac orifices and the insufficiency of the valves, the cardiac muscle redoubling its efforts to overcome the contraction of the orifices, and to struggle against the insufficiency of the valves. We then have *physiological* hypertrophy of the heart. But sooner or later, the efforts of the muscle become exhausted, and are powerless to overcome the constantly increasing obstacles. From this time, the physician detects all the general

symptoms of chronic disease of the heart. But do not believe, Gentlemen, that the heart quickly abandons the struggle. Clinical observation will inform you, that the disorder in the pulsations of the heart may disappear, and that for a variable period it may recover an energetic power, especially if a critical evacuation by the intestines or (as more frequently occurs) by the kidneys relieve the vascular system from dropsical pressure. We can very frequently prolong the life of the patient by exciting an abundant diuresis, and so restoring some of the power of the cardiac muscle.

In the immense majority of cases, the endocardium is affected after the articulations; but it sometimes happens, quite exceptionally, that the order of events is reversed, and that the law of Bouillaud is verified in an inverse sense; or in other words, that the rheumatism first attacks the endocardium, and then the joints. I had three such cases during the course of the year 1864.

A young man was admitted to Saint-Agnes's ward with high fever, and great general discomfort, in whom the only local morbid symptom was a somewhat intense blowing sound at the apex of the heart. Had this sound been heard only at the base of the heart, I might have attributed it to anaemia; but as it was, I had no hesitation in regarding it as evidence of endocarditis. Four days after admission, the knees became swollen and painful, and subsequently the shoulders were affected in a similar manner; and finally, the young man had all the symptoms of acute multiarticular rheumatism of average intensity. The patient recovered, but when he left our wards had a blowing sound, the very characteristic roughness of which sufficiently proved both the exactness of the diagnosis as to the anterior acute attack, and the existence of a contracted state of the left auriculo-ventricular opening, with insufficiency of the auriculo-ventricular valve.

The second case was that of a woman, aged 38, who occupied bed 11 of Saint-Bernard's ward. She had never had rheumatic arthritis at the date of her experiencing, three years ago, palpitation of the heart: she had a small, rather frequent cough, with dyspnoea, but without hemoptysis. The cardiac disturbance became at length so great, that she resolved, a year ago, to go into Professor Bouillaud's wards in La Charité. At that time, the distinguished professor detected a cardiac affection, for which he subjected the patient to active treatment. I beg your special attention to this case, because it shows you that the signs of which I have just been speaking have been observed by Bouillaud, and that like me he has attributed them to a lesion of the endocardium.

I shall now describe the affection for which this patient was admitted to my wards. Fifteen days before admission, she—*never before having had pains in the joints*—felt acute pain in the left knee, which became red and swollen; and she was unable to walk. On admission, the knee had ceased to be painful; but there were swelling, redness, and pain in the tarsal articulations, extending along the synovial sheaths of the tendons of the left foot and left thumb.

On examining the heart, I perceived, at the apex, accompanying the first sound, a blowing sound, which was very strong and rasping. This blowing sound was not heard at the base of the heart, and was not continued into the aorta. The pulse was small, and exceedingly irregular. The heart was considerably increased in volume. The liver, also, was very large. The respiratory sounds were everywhere natural, and, notwithstanding the cough, there was no pulmonary congestion.

The intensity and roughness of the blowing sound, its maximum intensity being at the apex, and the smallness and irregularity of the pulse concurred to lead me to diagnose an affection of the heart; the view I adopted being, that there was contraction of the left auriculo-ventricular opening, and insufficiency of the mitral valve. The diagnosis, supported by the existence of congestion of the liver, was confirmed by the previous diagnosis of Professor Bouillaud.

I have no doubt that this woman has an organic disease of the heart: that this disease had endocarditis as its starting point: and that the endocarditis, which was of old date, had been latent: finally, that it was proved to be rheumatic endocarditis by the arthritis which you had the opportunity of observing. The point in this case to which I desire specially to direct your attention is the existence of the cardiac prior to the articular manifestations...

I now wish, Gentlemen, to speak to you of a connection which exists between rheumatism and *erysipelas*. There is not only an analogy between the two diseases which are only seemingly inflammatory, but there is likewise a corelation. Not only have they the same migratory character, but the one may replace the other; as, for example, rheumatism may succeed erysipelas. At present, we have a simultaneous epidemic of erysipelas and rheumatism.

A young girl who lay in bed 8, Saint-Bernard's ward, was suddenly seized by rheumatic pains, when convalescent from severe erysipelas of the face. This patient, aged twenty-two, had already had, according to her own statements, very frequent erysipelatous attacks. The convalescence from the rheumatism did not go on satisfactorily: there was

a vague feeling of discomfort, and some fever in the evening. After two days of these undecided symptoms, she had acute pain in the knees, and an exacerbation of fever in the evening. Next day, the joints were swollen. Two days later, there was heard a *bruit de souffle* at the base of the heart, accompanying the first sound: it was not a soft blowing, due to anaemia, but a rough blowing which was evidently endocardiac. After the knees, the elbows, then the wrists and fingers were seized: in turn, the ankles and toes were attacked. At the present moment, the patient is in a really alarming state: in the evening, her pulse is about 120: her pains are excruciating: her appetite is gone: and during the eleven days which have elapsed since the rheumatism broke out, I have accomplished nothing by the treatment employed.

I cannot resist placing side by side the phenomena which we observe here after erysipelas with those so often seen after *scarlatina*, and (though more seldom) after nodular rheumatism. I have told you how common it is to see acute articular rheumatism, as well as pericarditis and endocarditis, during the convalescence from scarlatina. Now, erysipelas is an affection in which the skin is implicated as in scarlatina: erysipelas, which presents stronger affinities with fevers than with the phlegmasiae, possesses, like scarlatina and nodular erythema, a tendency to be followed by rheumatism associated with endocarditis.

You no doubt recollect what I said regarding the relations of *chorea* to rheumatism. You know that rheumatism is one of the most powerful predisposing causes of chorea. In the majority of cases adduced in support of this law of co-relation, the rheumatism precedes, at a longer or shorter interval, the appearance of the chorea. I have sometimes, however, been able reciprocally to announce the more or less speedy advent of articular rheumatism in children brought to me with chorea; and the result has justified my unfavourable prediction. Extend the induction to its extreme limits, and consider that since chorea, (a rheumatic affection), may precede arthritis of the same nature, it may quite as well, and for the same diathesic reasons, precede or accompany endocarditis. This conclusion, derived from the most legitimate induction, is confirmed by clinical observation. You recently saw in bed 25, Saint-Bernard's ward, a girl of sixteen with a first attack of chorea. On admission, the chorea was of eight days' duration: but she had had previously about three weeks of general discomfort, feverishness, insomnia, and loss of appetite. Three days afterwards, she experienced slight pain at the heart, unaccompanied, however, by palpitation or dyspnoea. This young woman has never had articular pains. The chorea is of average severity and is most intense on the left side, where there is anaesthesia and great debility. Guided by analogy, I auscultated the heart with much care; and had no difficulty in hearing a rough blowing sound at the apex. This patient, therefore, has had endocarditis at the same time as chorea. The rheumatism in this case, in place of attacking the articulations, attacked the endocardium, the law of co-relation being therefore only indirectly confirmed. This case is in harmony with an observation made by Dr. Henri Roger. In his clinical lectures at the Hôpital des Enfans Malades, this judicious observer has recently stated that in at least one fourth of all the cases of chorea which he has observed, there were heart complications, either with or without rheumatism...

It sometimes happens, Gentlemen, that the viscera are primarily invaded by rheumatism. There is, as you know, a form of pneumonia called *rheumatic pneumonia*, which sometimes occurs with all the physical and rational signs of inflammatory pneumonia—the stitch in the side, cough, difficult breathing, bloody expectoration, dulness, râles, and blowing—in fact, every symptom and every physical sign. But that which gives this kind of pneumonia its distinctive character, and makes it a species, is that all the symptoms of pneumonia may suddenly disappear without the gradual decrease observed in inflammatory pneumonia. At other times, the patients have a stitch in the side, oppression, crepitant and subcrepitant râles, and blowing, while the expectoration is merely viscous or catarrhal, and presents no trace of blood. The rheumatic disease may remain confined to the lung; but it is not unusual for articular pains to occur on the cessation of the symptoms of pneumonia . . .

There is perhaps no acute disease which so rapidly induces *anaemia* as rheumatism. The extreme pallor, the vascular blowing, and the hydraemic fulness of the pulse declare the existence of a state of acute cachexia quite independent of the medical treatment which has been employed. But though the blood loses a notable quantity of its red globules, it acquires a large amount of fibrine during the acute stage of the disease. I am not prepared to say that the excess of fibrine increases the

plasticity of the blood; but the fibrinous productions deposited on the valves show that there is a great tendency to coagulation. Are we to believe that this excess of fibrine in the serum of the blood is the consequence of the supposed inflammatory element in rheumatism? It seems useless to discuss this question, wherefore I prefer simply to state the fact that along with the acute cachectic state of the patients there is very great *fibrination of the blood*. The crasis of blood is so much modified by acute rheumatism that months are required before the patients entirely recover their health . . .

* * *

Author's Comments

In the foregoing excerpt the valuable paragraphs on ulcerative endocarditis (now commonly called bacterial endocarditis) have been omitted for lack of space.

Trousseau recognized cold as a predisposing cause of rheumatic fever. He also believed that erysipelas, scarlet fever and erythema nodosum led to this disease.

His descriptions of rheumatic patients are up to his usual high standard. He does not omit to notice the individual drops of perspiration and the distinctive odor. He comments on the pallor of the face, sometimes tinged with dull blue. Following the explicit instructions of the Hippocratic school he depicts the posture of the patient in bed, mentioning especially the dread of movement. The descriptions of the affected joints include a number of finely observed details, e.g., that when the hand is swollen it may appear to be continuous with the forearm, anatomic lines of demarcation having disappeared in the edema.

With respect to rheumatic disease of the heart, Trousseau was inclined to accept Bouillaud's famous law of coincidence between articular rheumatism and heart disease.* He noted, however, that signs of heart disease were often absent in cases of rheumatic fever. He recognized also that there were patients with diseased mitral and aortic valves in whom no history of acute articular rheumatism could be elicited. He thought that some cases of heart disease were caused by alcoholism. His description of the progress of rheumatic heart disease is charming in the Gallic manner ("But do not believe, Gentlemen, that the heart quickly abandons the struggle."). He speaks of diuresis in typical Hippocratic terms as a critical evacuation by the kidneys. This he says relieves the vascular system from dropsical pressure.

* Jarcho, S. Rheumatic carditis: Bouillaud and some unkown Irish precursors. *Am. J. Cardiol.*, 1: 514, 1958.

Case Reports

Chronic Subclavian-Carotid Artery Obstruction Syndrome

Report of a Patient with Coarctation of the Aorta and Rupture of an Associated Traumatic Aneurysm of the Aortic Arch*

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THE ABSENCE or diminution of pulses in the arms and neck is a physical sign which in the past has been referred to as "anisosphygmia," "pulsus incongruens" and "pulsus differens."[1] Such changes in the peripheral pulses, preferably described rather than so titled, represent the classic feature of chronic disease of the great vessels arising from the aortic arch or of the arch itself.

"Takayasu's disease," an eponymic designation for the Japanese physician who recorded this syndrome in 1908, refers to a non-specific arteritis resulting in absent radial pulses, changes in the eyes and central nervous system manifestations in young women of his country.[2] "Reverse coarctation" was the name suggested by Griffin[3] in 1939 to indicate the absence of pulsations in the upper extremities with elevation of the blood pressure in the lower extremities, in contradistinction to the usual findings of coarctation. By its outstanding clinical feature, this syndrome has also come to be known as "pulseless disease." Frovig[4] and Ross and McKusick[5] used the more inclusive term "aortic arch syndromes" to include a wide range of pathologic changes occurring in the aortic arch and its branches that might account for alterations in one or more of the pulses under consideration. The term "chronic subclavian-carotid artery obstruction syndrome" most completely describes the entity characterized by involvement of all cervical and upper extremity pulses with its catholic manifestations.

The present report represents a well documented account of such a disorder of the great vessels in a twenty-eight year old man. This case is unusual because of inordinate calcification of the arch of the aorta, an associated traumatic aneurysm with terminal rupture and the presence of coarctation of the aorta of the adult type.

CASE REPORT

A twenty-eight year old white man was admitted to the medical service of St. Alexis Hospital on March 3, 1958, with a chief complaint of pain in the left shoulder.

The patient's history revealed that in 1938 he had been hospitalized for enucleation of the right eye due to remote lye burns. At that time, a leukopenia of 1,000 per cu. mm. with a normal differential was present with normal red blood, hemoglobin and platelet counts. A bone marrow examination disclosed no abnormalities. No murmurs or abnormality of pulses were noted.

In 1950, the patient was hospitalized for treatment of a fractured clavicle after an automobile accident. Subsequently, a military preinduction physical examination resulted in deferment. He was refused insurance the same year for unknown causes.

A nasal polypectomy was performed in 1955, at which time the blood pressure was recorded as 110/90 mm. Hg, but no mention was made of abnormalities of the pulse. No laboratory procedures were performed.

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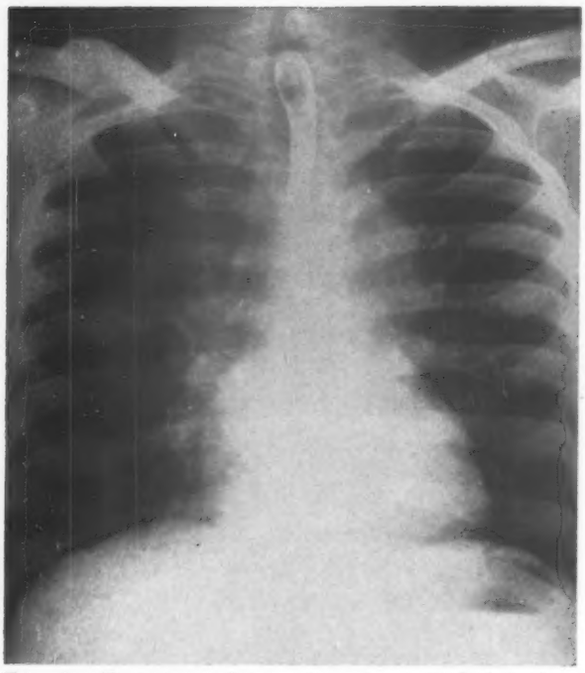

FIG. 1. Posteroanterior roentgenogram of the chest following barium swallow, showing aneurysmal dilatation of the aorta in the region of the aortic knob.

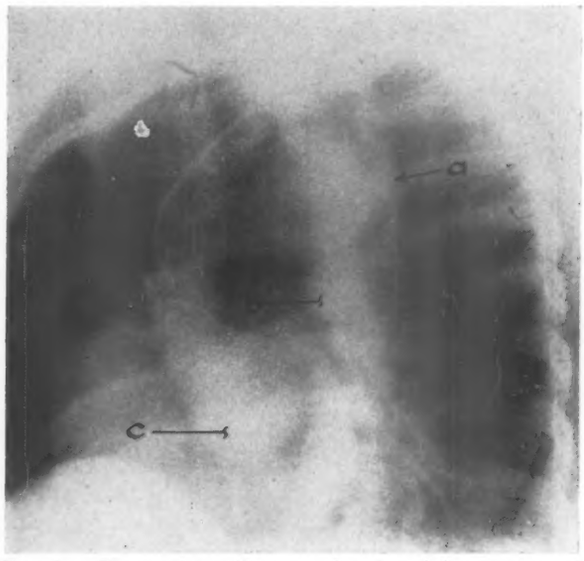

FIG. 2. Cineangiocardiogram showing (a) aneurysmal dilatation of aorta just beyond the left subclavian artery, (b) normal aorta below the site of coarctation and (c) left ventricle.

Six months prior to the present admission the patient began to have periodic episodes of pain in the left shoulder accompanied by fever and chills. The attacks lasted from one to three days and subsided with periods of rest without specific medication. One month prior to admission the patient struck his chest against the steering post of his automobile in an accident. He continued to be gainfully employed as an automobile mechanic until two weeks prior to admission. Four days prior to admission, pain in the left shoulder occurred with increased severity and was accompanied by fever, chills and shortness of breath. For forty-eight hours prior to admission, hoarseness was present.

Examination: The patient was a well developed, thin, adult white man in acute distress with pain in the left shoulder. The temperature was 100.2° F., and the heart rate was 120 per minute. A right ocular prosthesis was present. The left fundus was normal except for physiologic demyelinization of the nerve fibers about the disc. Neither pulse nor blood pressure was obtainable in the upper extremities. The blood pressure in the lower extremities was 170/110 mm. Hg. Markedly diminished carotid pulsations were present bilaterally. There was a tracheal tug with a definite systolic shock in the suprasternal notch. A paralysis of the left recurrent laryngeal nerve was present. The right clavicle was deformed. Chest expansion was equal bilaterally. The lungs were normally resonant to percussion, and rales were audible in the lower one-third of both lung fields. The heart was not enlarged. The apex beat was forceful. A harsh grade 3 blowing systolic murmur was audible at the base of the heart. The aortic second sound was intact.

The femoral and peripheral lower extremity pulses were readily palpable. There was no edema, cyanosis or clubbing. Development and strength of the muscles in all extremities were normal. The skin was warm without evidence of trophic change.

Laboratory Findings: Results of laboratory examinations were as follows: Hemoglobin 12.2 gm. per cent, white blood count 2,500 per cu. mm. with 48 per cent segmented neutrophils, 26 per cent band cells, 1 per cent basophils, 16 per cent lymphocytes, 3 per cent monocytes, 4 per cent metamyelocytes and 2 per cent myelocytes. The urine was normal, and the serologic test for syphilis gave negative results. An electrocardiogram showed a sinus tachycardia and left ventricular hypertrophy. The total protein and albumin/globulin ratio were normal as were the blood sugar and blood urea nitrogen. A lupus erythematosus cell preparation was negative. A roentgenogram of the chest showed a poorly delineated aortic knob and an area suggestive of a mediastinal mass (Fig. 1).

Course: The patient was transferred to St. Luke's Hospital for cardiac catheterization and cineangiocardiograms. Results of the cardiac catheterization studies were normal. Cineangiocardiograms (Fig. 2) revealed the presence of a calcified aneurysm of the aortic arch just distal to the origin of the left subclavian artery. Calcification of the great vessels was present as well. The patient was discharged asymptomatic to remain at home while arrangements were being made for an attempted resection of the aneurysm.

He was readmitted to St. Luke's Hospital on an emergency basis four days following discharge. The physical findings were unchanged. The day after

admission, he coughed up large quantities of blood, and died.

POSTMORTEM FINDINGS

Lungs: The right lung weighed 590 gm., the left 650 gm. On cut section the dependent portions of the lungs contained large amounts of aspirated blood, and clots were seen within the tracheobronchial tree and in the smaller bronchioles on the cut surface. There was parenchymal hemorrhage in the apex of the left lung where an aneurysm of the arch of the aorta had eroded into the parenchyma of the lung. There was a large blood-filled cavity measuring approximately 4 cm. in diameter in the left upper lobe at the site of rupture (Fig. 3). The parenchyma of the lung in this area was greatly engorged with blood. There was some thickening of the pleura and the lung over the area adjacent to the aneurysm.

Heart: The heart was opened *in situ* and showed only postmortem blood clots. The thickness of the right ventricular wall was 0.5 cm.; the thickness of the left ventricular wall was 1.8 cm. There was some sclerosis of the aortic valve and the sinuses of Valsalva. The aorta above the valve showed considerable atherosclerotic changes with calcification (Fig. 4). The valve cusps were shortened, and adhesions between them produced a slight stenosis of the aortic valve. The ostia of the coronary arteries were involved in the formation of the atheromatous plaques.

Aorta and Branches: A coarctation of the aorta was seen at a level just distal to the left subclavian artery. The superior and posterior surfaces of the aortic arch distal to the innominate artery, involving that portion of the aorta from which the left subclavian arose, were involved in a saccular aneurysm which was lined by a laminated old blood clot. This aneurysm measured 5 by 6 cm. in diameter and had ruptured into the lung as described. The innominate artery and its branches were virtually occluded by calcified atheromatous plaque formation as were the left common carotid and left subclavian arteries. Below the coarctation, the aorta was normal in appearance. The coarctation did not occlude the lumen as completely as usual, but reduced the opening to a diameter of 1 cm.

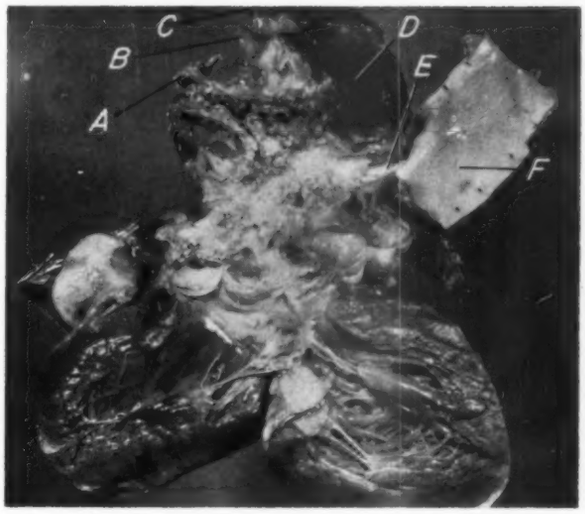

FIG. 4. Specimen of the heart and of the thoracic aorta and its branches showing calcification in the ascending aorta and the arch, with a normal descending aorta. Note the calcification in the innominate artery, and the traumatic aneurysm above the level of the coarctation obstructing the left subclavian artery. A, innominate artery. B, left carotid artery. C, left subclavian artery. D, traumatic aneurysm. E, area of coarctation. F, normal descending thoracic aorta.

The anatomic diagnoses were as follows:

(1) Coarctation of the aorta with rupture of a sac-

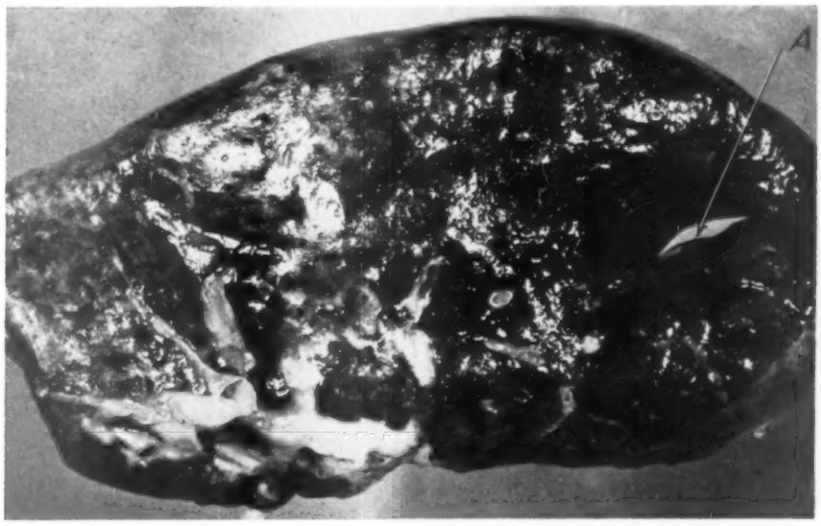

FIG. 3. Section of lung showing infiltration of the left upper lobe with blood, and the cavity (A) produced by rupture of the traumatic aneurysm into the lung.

cular aneurysm into the left lung; calcification of the arch of the aorta and major branches; cardiac hypertrophy (450 gm.); and hydropericardium (100 cc.);

(2) Bilateral focal and confluent intra-alveolar pulmonary hemorrhages; left hemohydrothorax (100 cc.);

(3) Reactive fibroplasia in the left pleura;

(4) Focal renal glomerular hyalinization with calcification of renal arteries and renal cytomegaly;

(5) Chronic passive congestion of the liver;

(6) Focal non-caseating granulomas of the mediastinal nodes (etiology not determined);

(7) Remote fracture of the right clavicle; and

(8) Remote enucleation in the right orbit.

Comments

As late as 1954 Bustamante et al.[6] reported only seven cases of this entity from the literature in which a complete autopsy report was available. This case is interesting not only from the standpoint of having an unusual complication of a rather rare clinical entity, but also because of the complete pre- and postmortem studies available. The outstanding features of the postmortem examination of this patient were: (1) abnormal calcification of the aortic arch and its branches in a twenty-eight year old man; (2) a ruptured traumatic aneurysm of the arch just beyond the left subclavian artery; and (3) coarctation of the aorta. One must necessarily conclude from these findings that extensive atherosclerosis of the aortic arch and its branches accounted for the loss of pulses in the upper extremities and neck of this patient.

Etiology of Aortic Arch Disease: Ross and McKusick[5] discussed a variety of etiologic factors to explain the wide range of symptoms that may be present in aortic arch disease. They include any pathologic process of the arch or its branches which might diminish or obliterate one or more of the pulses in the neck or upper extremities. Among those described are:

(1) Syphilitic aortitis with aneurysm;
(2) Syphilitic aortitis without aneurysm;
(3) Atheromatosis;
(4) Trauma with aneurysm;
(5) Trauma without aneurysm;
(6) Congenital anomalies;
(7) Chronic dissection of the aorta;
(8) Thrombophilia;
(9) Non-specific arteritis;
(10) Embolism;
(11) Extravascular upper mediastinal tumor; and
(12) Cases of obscure nature.

It is interesting to note that these authors conclude, from studying one hundred cases of aortic arch syndromes taken from the literature, as well as thirty-five of their own, that *atherosclerosis* is a rare cause of this disorder. In their own thirty-five cases, only five could be traced to this cause. These, moreover, were incomplete obstructions or involved the loss of pulsations in the left arm only. In addition, their patients with atherosclerosis were all over the age of fifty years with the exception of one who was just below this age, in contrast to the patient described in this report who was only twenty-eight years old.

Of the seven patients with this syndrome who came to autopsy reviewed by Bustamante and associates, only one had atheromatous occlusions of the ostia of the great vessels of the arch, while three had syphilitic aneurysms and three were shown to have arteritis. These findings again emphasize the heretofore relatively unimportant role assigned to atherosclerosis as a basis for this syndrome.

Trauma, either with or without formation of aneurysm, has been stressed in the etiology of chronic subclavian-carotid occlusion. Whereas this young man had a history of two distinct instances of injury to the anterior wall of the chest, it is difficult to evaluate the precise role of trauma in the development of his ultimate clinical picture. When assessing trauma as a cause for diminution or absence of pulses in the upper extremities, occlusion of the ostia of the major vessels arising from the aortic arch by a traumatic or dissecting aneurysm is easy to explain. It is, however, somewhat more difficult to imagine anything but direct trauma hastening an atheromatous process in a vessel, or predisposing the entire vessel or a portion of the vessel to atherosclerosis. In most of the cases reported, the causal relation of trauma to the ultimate clinical picture was purely speculative. Again, Bustamante states that no record of a patient who came to autopsy in whom the etiology wasother than syphilis, atheroma or arteritis of unknown cause was found.

Haas[7] and others[8,9] have demonstrated the relation of sudden changes in velocity to the production of trauma to the aorta. The aorta is fixed at its attachment to the heart and at the ligamentum arteriosum, but otherwise it is a free structure subject to displacement and buckling under sudden change of direction. The most frequent points of rupture are the posterior wall in the vicinity of the ligamentum

arteriosum or in the posterior wall just proximal to the aortic valves. By determining the degree of elasticity of the aorta at the time of impact or velocity change, the state of the heart in systole or diastole may play a role in the extent of the aortic injury.[10]

In the present case, it is interesting to note that in the postmortem specimen the severe sclerotic changes were limited to that portion of the thoracic aorta above the coarcted segment. Since the coarctation was not severe, it might be speculated that at the time of the original injury to the chest wall, seven years prior to the second injury, a tear in the intima or a partial break in the aortic wall resulted, which healed in such a manner that acquired coarctation developed. This, in turn, might have led to early hypertension in the upper extremities and the severe atherosclerotic changes found in the aortic arch and its branches at postmortem examination. The vulnerable sclerotic aorta then tore completely at the time of the second blow to the chest and the fatal traumatic aneurysm resulted. Although this coarctation was located in the usual site, it was not so complete as the usual, symptomatic, congenital coarctation.

Kampmeier and Neumann[11] first suggested that *congenital abnormalities* in the vicinity of the aortic arch may predispose to the development of occlusive disease of the arch and its branches. Most anomalies of the aortic arch represent merely differences in the course of flow of blood and not resistance to this flow, and would not appear to induce premature atheromatous change. Coarctation of the aorta has not as yet been suggested as an underlying cause of the chronic subclavian-carotid artery syndrome.

Aggeler, Lucia and Thompson[12] reported an instance of this syndrome in which primary thrombocytosis and autohemagglutination were prevalent features. The relationship of *hematologic disorders* to the production of vascular obstruction is not completely appreciated. Similarly, in our patient no relationship is recognized between the lesions described and the leukopenia found in infancy and again shortly before his death.

Clinical Features: As the etiology of this clinical entity may be any process obstructing flow through the major branches of the aortic arch, so may the symptoms be any that reflect this reduction in blood flow through the narrowed vessels. The pulses in the upper extremities become imperceptible prior to complete obliteration of the blood pressure, and the absence of pulsations does not necessarily indicate a cessation of flow. Prominence of the collateral arterial circulation has been noted frequently, most often by the presence of a bruit at the base of the neck, or by tortuous vessels over the back of the chest with roentgenographic evidence of erosion of the ribs as reported in the patient of Weir and Kyle.[13]

Trophic changes in the reported cases have been limited to the head and its appendages, but interestingly enough they have not occurred in the upper extremities. Hypertension in the lower extremities is present frequently.

The cerebral symptoms are those that would be anticipated with internal carotid artery thrombosis, the major symptoms consisting of vertigo when arising from a sitting or lying position, episodic loss of consciousness, hemiparesis or hemiplegia, and convulsions. Visual disturbances of a transient nature resulting from a reduction in blood flow during changes from a supine to an erect position, or with exertion, range from slight diminution of visual acuity to complete amaurosis. They may be a common occurrence. Early development of cataracts and retinal atrophy with pigmentation have been described.[5]

Cardiac abnormalities are not infrequently present, due to primary or secondary hypertension, syphilitic involvement of the base of the aorta or independent arteriosclerotic coronary artery disease. The electrocardiogram will, of course, reflect those abnormalities produced by the basic heart disease, but may be perfectly normal. Systolic murmurs at the base of the heart are frequently present, and diastolic murmurs suggesting arteriovenous shunts have been described.[14]

Summary

Report of a patient with "chronic subclavian-carotid artery obstruction syndrome" due to extensive arteriosclerosis of the aortic arch and its branches, associated with coarctation of the aorta and a traumatic aneurysm with terminal rupture, is presented.

The possibility of remote trauma as a prime causative factor in the production of the syndrome in this patient is discussed.

Acknowledgment

Special acknowledgment is given to Drs. G. W Wright and H. F. Inderlied, St. Luke's Hospital

Cleveland, Ohio, for assistance in the diagnostic studies performed.

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Combined Congenital Pulmonic and Aortic Stenosis*

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THE coincidental occurrence of pulmonic stenosis and aortic stenosis of congenital origin in the same patient is almost unknown in literature. To the best of our knowledge the first case of congenital heart disease with this combination was reported only recently.[1] Because of its rarity, we deem it worthwhile to report a similar case and to point out the diagnostic problems encountered.

CASE REPORT

S. J., a ten year old girl, was admitted to the Tel-Hashomer Government Hospital on June 6, 1957, for cardiac studies. Her mother had no illness during the pregnancy and the birth was uneventful. Five siblings are alive and in good health. At the age of two weeks the signs of a heart lesion were noted. The patient's physical and mental development were retarded; she began to walk at the age of five years and at present she is only in the second grade at school.

She has had tonsillitis, but there is no history of rheumatic fever. Cyanosis has never been observed. During the last year she has tired easily at play. Attacks of coughing have occurred, especially after exercise and at night.

Physical examination: The patient was a moderately well developed delicate child with mongoloid facies, thick everted lips, widened nostrils and mild prognathism. Clubbing and cyanosis were absent. There was moderate deformity of the thoracic cage with a prominent angle of Louis and mild funnel chest lower down.

All the peripheral pulses were present and the cardiac rhythm was regular. The blood pressure was 130/80 mm. Hg. The beat at the apex was palpable in the fifth intercostal space in the midclavicular line and a systolic thrill was felt over the pulmonic area and the suprasternal notch. A loud, coarse systolic grade 4 murmur of ejection type was audible over the precordium, maximal in the pulmonic area; the second pulmonary sound was heard faintly. Over the aortic area, in addition to the systolic murmur, there was a short, blowing diastolic murmur and the second aortic sound was diminished. The systolic murmur radiated to both sides of the neck. These findings were confirmed by phonocardiography.

The lungs were clear to auscultation. The liver was palpable. There was no peripheral edema.

Laboratory Findings: The hemoglobin was 15.2 gm. per cent and the hematocrit 41 per cent. All other routine laboratory examinations were normal.

The electrocardiogram (Fig. 1) showed sinus rhythm and transient nodal rhythm; there were signs of right ventricular hypertrophy. The deep S waves in leads V_2 and V_3, being unusual in pulmonic stenosis,

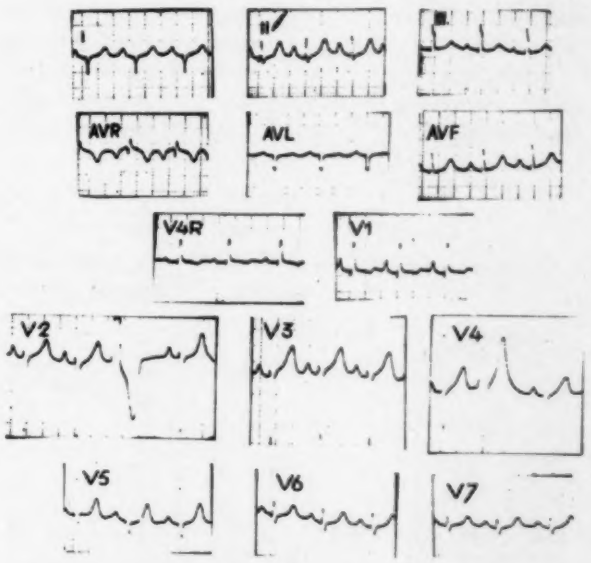

FIG. 1. *Electrocardiographic findings:* Sinus rhythm, right axis deviation (axis +110°). Prolonged P-R interval (0.20 second). In aVR a QR pattern with a Q/R ratio of 1. High R waves in leads V_4R and V_1. Deep S waves in leads V_2 and V_3. QR waves in leads V_5 and V_6 with small widened S waves. $S(V_2) + R(V_5) = 38$ mm.

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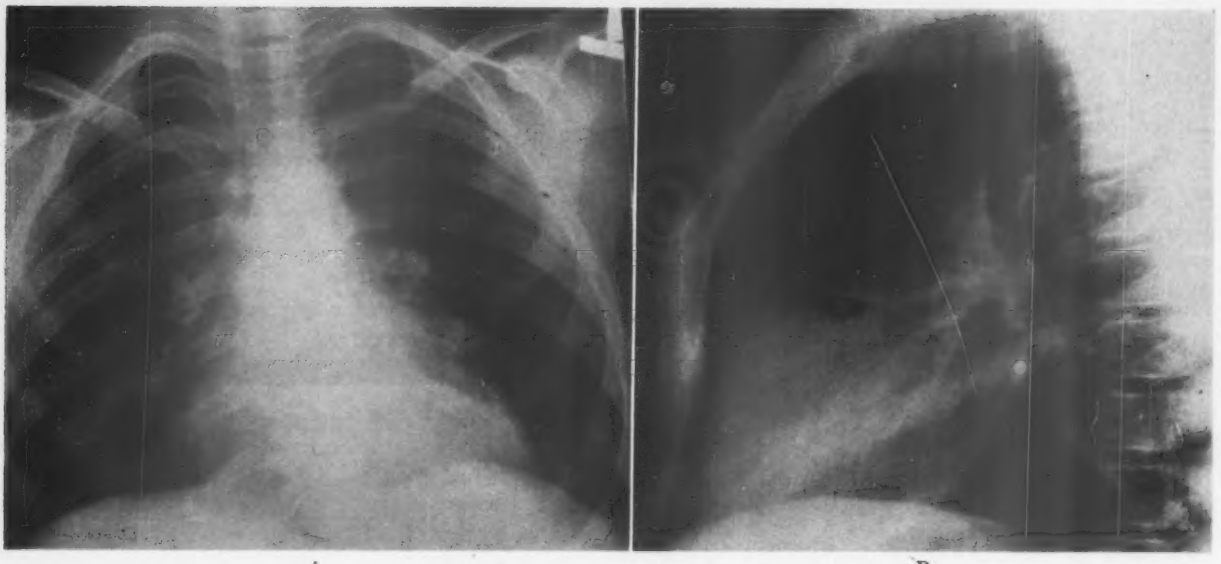

A B

FIG. 2. *Roentgenograms of the chest* in posteroanterior (A) and left lateral projection (B). Note normal lung vascularity, enlarged right ventricle with increased contiguity of surface to the bulging anterior thoracic wall, and slightly widened aorta.

raised the suspicion of left ventricular hypertrophy.

Radiologically, the pulmonary vascularity was within normal range. There was slight cardiac enlargement, predominantly in the right ventricle. Upon fluoroscopy, large pulsations were seen in the ascending aorta. No calcifications were observed (Fig. 2).

From these physical findings the diagnosis of pulmonic stenosis was considered. The presence of a blowing diastolic murmur over the left sternal border together with the marked pulsation of the ascending aorta seen during fluoroscopy and the electrocardiographic findings raised the suspicion of aortic valve involvement.

TABLE I
Cardiac Catheterization Findings

Location of Catheter	Pressure (mm. Hg)		Oxygen Saturation*	
	S/D	Mean	Photometry (%)	Van Slyke (vol. %)
Superior vena cava	...	...	72	...
Inferior vena cava	...	...	78	...
Right atrium	10/0	5	74	...
Mid right ventricle	105–110/0	43	69	...
Right ventricular outflow tract	50/0	...	70	11.6
Main pulmonary artery	15–20/7–10	16	71	...
Right pulmonary artery	15–20/7–10	16	72	...
Pulmonary artery wedge	8–15	...	98	...
Femoral artery	100–110/65–75	90	96	14.8

* The oxygen measurements were made with the aid of the Brinkman-Kipp Haemoreflector.

Right Heart Catheterization: The results are shown in Table I.

The absence of abnormal findings in the oxygenated blood in various chambers of the heart excluded the presence of a significant left-to-right shunt and the absence of desaturation of the peripheral arterial blood excluded a right-to-left shunt. The pressure tracing during the withdrawal of the catheter from the pulmonary artery into the right ventricle showed pressure gradients between the pulmonary artery and the outflow tract of the right ventricle as well as between the right ventricular outflow tract and the right ventricle (Fig. 3). These findings indicated pulmonic stenosis, both valvular and infundibular, with the presence of an infundibular chamber.

Left Heart Catheterization: The left ventricle and the femoral artery were simultaneously punctured. The pressure in the left ventricle, according to the technic described by Brock, Milstein and Ross,[2] was 160/5 mm. Hg and in the femoral artery 125/85 mm. Hg. The systolic gradient was 35 mm. Hg (Fig. 4). In the pressure tracing of the brachial artery the prolonged ejection time (0.09 second) and the anacrotic notch with typical plateau curve served as additional evidence in favor of the diagnosis of aortic stenosis.

Angiocardiography: Venous angiocardiography was performed next (Fig. 5). Marked dilatation of the subvalvular region suggestive of an infundibular chamber; eccentrically fixed, dome-like pulmonary

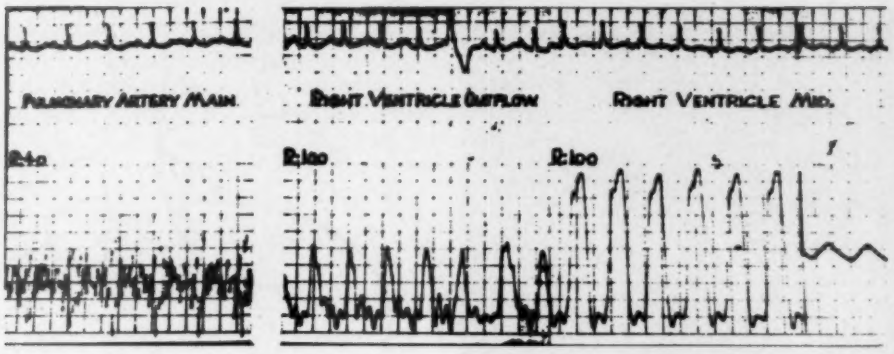

FIG. 3. *Right heart catheterization:* Pressure tracing during the withdrawal of the catheter showing the difference in pressures between the pulmonary artery, the right ventricular outflow tract and the right ventricle itself.

valves and moderate poststenotic dilatation of the main pulmonary artery were seen. The aortic valves appeared fixed and there was widening of the ascending aorta.

The findings on angiocardiography were interpreted as indicative of pulmonic stenosis, valvular and most probably infundibular, and aortic stenosis.

COMMENTS

It seemed to us that the diagnosis of pulmonic stenosis, both valvular and infundibular, with an intact ventricular septum had been verified by right heart catheterization and supported by the angiocardiography. The left ventricular puncture and the pressure tracing curve of the femoral artery and the pressure gradient between them, are strong evidence for aortic stenosis. As in the single similar case previously reported,[1] we could not distinguish, on the basis of our investigation, between aortic and subaortic stenosis. The diastolic murmur over the aortic area occurs in about 30 per cent of cases of aortic stenosis, subvalvular as well as valvular.[7] Neither could we, on the basis of the angiocardiograms, give a clear-cut answer to this question. The majority of the authors[3–5] stressed their inability to distinguish between these two conditions by clinical and/or other investigations, and this is our experience as well. The question arises as to the possibility of the aortic stenosis being rheumatic in origin in this patient with congenital pulmonic stenosis. Against this possibility are the absence of a previous rheumatic history and the rarity of significant hemodynamic effects in rheumatic aortic stenosis at this age.

According to the clinical and laboratory findings, the pulmonic stenosis seemed to be the predominant lesion. The pressure gradient of 35 mm. Hg between the left ventricle and the aorta is actually higher, according to Kroeker and Wood,[6] because the femoral artery pressure was 10 to 15 mm. Hg higher than the aortic pressure. This means that in our patient the real pressure gradient is about 50 instead of 35 mm. Hg.

The diagnosis of congenital pulmonic stenosis, valvular and infundibular, and aortic stenosis appears to be substantiated by the conformity between the clinical features and the results of the special tests. This combination of congen-

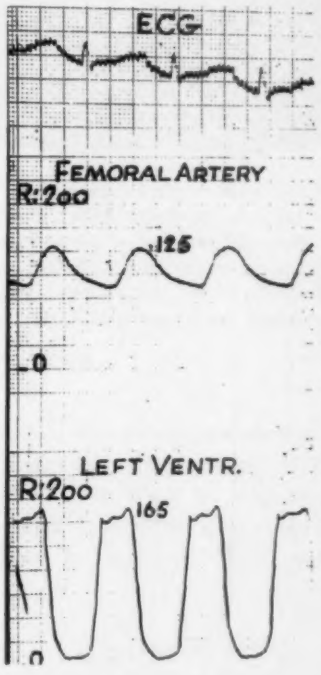

FIG. 4. *Left ventricular puncture:* Simultaneous pressure tracing of left ventricle and femoral artery showing systolic gradient of 35 mm. Hg.

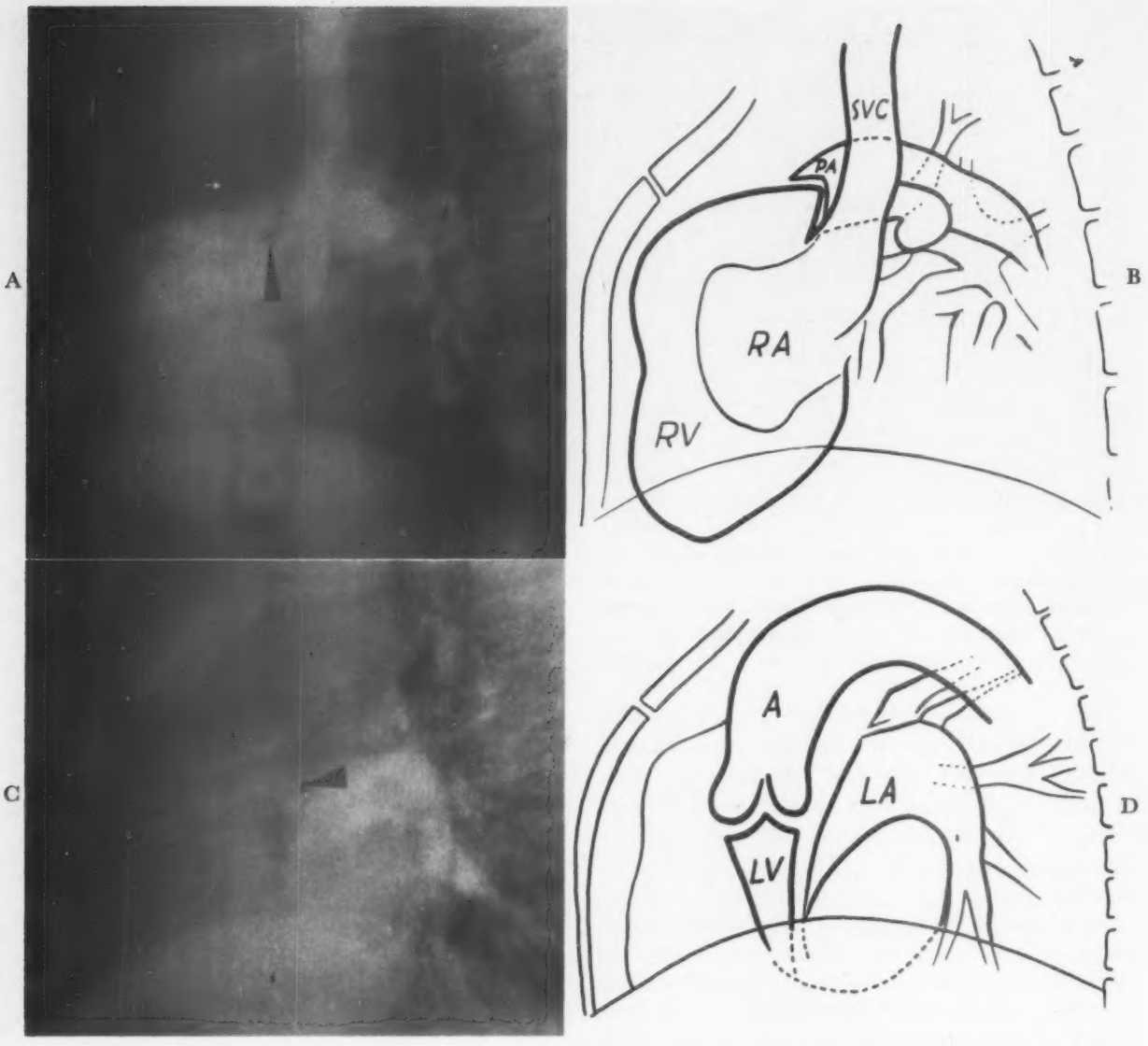

FIG. 5. *Angiocardiogram in lateral projection.* A, film at one and a half seconds reveals fixed pulmonary valves with a conical shape and eccentrically directed apex (arrow). The cusps appear thickened, especially the posterior one. Marked dilatation and bulging of the outflow of the right ventricle suggestive of an infundibular chamber; (the ostium infundibuli is obscured by the opacified right atrium). Moderate poststenotic dilatation of the main pulmonary artery. B, diagram of A. C, at five seconds, the aortic valves are well visualized and fixed (arrow). Note widening of the ascending aorta and prolonged left heart opacification. D, diagram of C.

ital heart lesions seems to be extremely rare; this is the first case we have encountered. The surgical approach in such a case has to be a procedure correcting both stenotic lesions under direct vision, with the use of extracorporeal circulation.

SUMMARY

A case of combined congenital pulmonic stenosis, valvular and infundibular, and aortic stenosis with an intact ventricular septum is presented. The pulmonic stenosis appeared as the predominant lesion. The diagnosis was established on the bases of clinical, physiologic and roentgenologic findings. The rarity of this combination is emphasized.

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Diagnostic Shelf

Aortic Stenosis vs. Syphilitic Aortitis*

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Chicago, Illinois

A THIRTY-SIX year old Negro woman was admitted to the hospital in December 1958 complaining of increasing dyspnea on exertion and rather severe orthopnea of approximately two years' duration. She also had frequent attacks of paroxysmal nocturnal dyspnea. No swelling of the legs or pain in the chest had been noted.

The patient had contracted syphilis in 1946 for which she received injections of a heavy metal for a period of six months.

More recent complaints were persistent, throbbing, frontal headache, accompanied by mild dizziness and occasional nausea and vomiting.

PHYSICAL EXAMINATION

Physical examination revealed a well nourished and well developed patient in no acute distress. Blood pressure was 180/60 mm. Hg; the pulse was regular, 80 and bounding (Corrigan pulse). There was no distention of the veins of the neck and peripheral edema was not present. The liver was not palpable. The lungs were clear.

The heart was enlarged to the left on percussion and the apical impulse was in the sixth intercostal space in the anterior axillary line. No thrills were palpable. There was a grade 3, harsh systolic murmur heard over the entire precordium. This was loudest along the left sternal border and transmitted upwards to the carotid arteries. This was followed by a grade 2, softer, blowing early diastolic murmur in decrescendo with similar distribution.

LABORATORY DATA

The hemogram was normal. The result of the serologic test for syphilis was 2 plus. The Wasserman reaction was negative. The urine contained a trace of protein, and the sediment, a few white blood cells and, on one occasion, 8 to 10 red blood cells. The protein-bound iodine was 6 μg. per 100 ml. of serum. The basal metabolic rate was plus 14. Spinal fluid pressure was 90 mm. water; white blood cells, 0; and protein, 27. Results of the Pandy and Kahn tests were negative. Chlorides were 740. The gold curve was 0 (10). Venous pressure was 174 mm. water and the Decholin® circulation time was 15 seconds.

GRAPHIC RECORDS

Roentgenograms: X-ray examination, including fluoroscopy and barium swallow, revealed diffuse cardiac enlargement with predominant enlargement of the left ventricle and some degree of diffuse dilatation of the aorta; no left atrial enlargement. The aortic indentation over the barium-filled esophagus was prominent.

Electrocardiogram: The record showed sinus rhythm, left axis deviation, and inverted T waves in leads I, II, aVL, V_4, V_5 and V_6.

Phonocardiogram: This tracing revealed a short systolic murmur with a few larger vibrations at mid-systole, over the aortic area. Over the

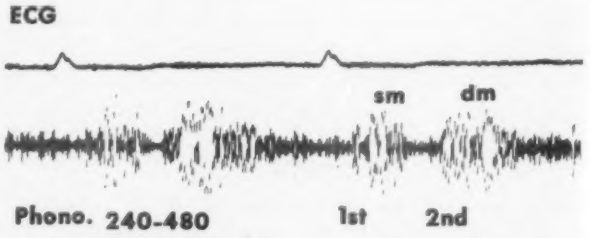

FIG. 1. Phonocardiogram over aortic area. *Above*, electrocardiogram. *Below*, phonocardiogram.

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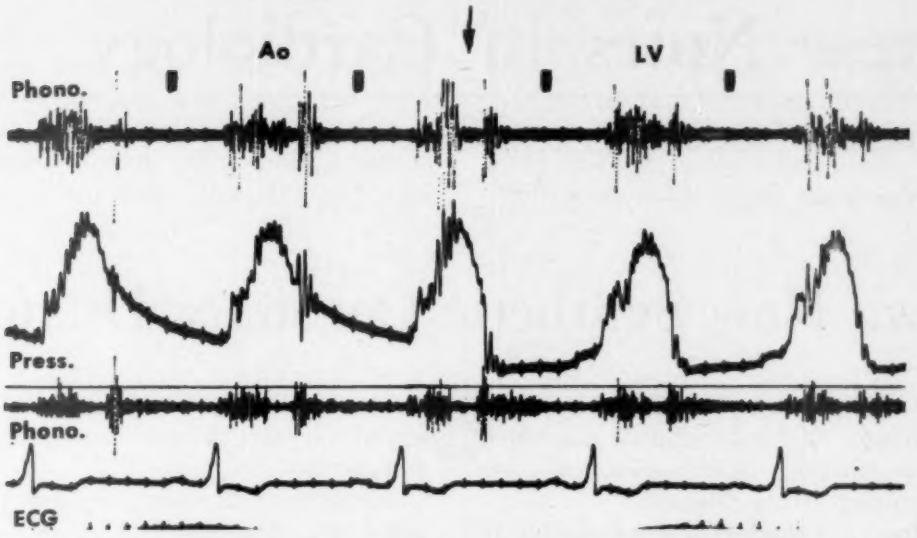

FIG. 2. Retrograde aortic and left ventricular catheterization. Advancement of catheter from aorta (first two waves) to left ventricle (last two waves). *From above*, intracardiac and vascular phonocardiogram; pressure tracing; zero line; precordial phonocardiogram; electrocardiogram. The arrow indicates the crossing of the aortic valve.

same area, there was a high-pitched, early diastolic murmur in decrescendo. The second sound was hardly visible over the aortic area, but the aortic component of this sound was well developed at the apex (Fig. 1).

Carotid Pulse Tracings: There was a rapid rise followed by an anacrotic depression and a late peak.

COMMENTS

The most likely diagnosis seemed that of "syphilitic aortitis, *relative* aortic stenosis, aortic insufficiency." However, several cardiologists questioned this diagnosis and thought the patient had rheumatic heart disease, aortic stenosis and insufficiency. For this reason, it was decided to perform retrograde left heart catheterization via the left brachial artery.

Left Heart Catheterization: Pressures: There was no systolic gradient across the aortic valve. This proved that there was no hemodynamically significant aortic stenosis (actually, the aortic systolic pressure [158 mm. Hg] was higher than that of the left ventricle [145 mm. Hg]). A low diastolic pressure in the aorta (42 mm. Hg) and a high diastolic pressure in the left ventricle (0.7 to 25.3 mm. Hg) were explained by the aortic insufficiency.

The pressure pattern of the left ventricle showed a typical slow rise which was explained as the result of incomplete closure of the aortic valve (valvular insufficiency) during the period of tension, plus the effect of a dilated and damaged aortic wall (Fig. 2).

The intracardiac and intravascular phonocardiograms revealed not only the systolic murmur, but also some vibrations in early diastole.

CONCLUSION

The final diagnosis was syphilitic aortitis, relative aortic stenosis and aortic insufficiency.

It should be stressed that in patients having a small A_2 with no history of syphilis, and in whom diagnosis is uncertain, retrograde aortic catheterization may be necessary. It is a harmless procedure if there is aortic insufficiency. It reveals whether or not there is a systolic gradient across the aortic valve, this gradient being evidence of an obstructive lesion.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Two New Synthetic Coronary Dilators

JEAN Sicé (Department of Pharmacology, The Chicago Medical School) has summarized experimental observations on two synthetic coronary artery dilators.

The first drug, 3,5-diiodo-4-hydroxyphenyl 2-ethyl-3-benzofuranyl ketone, or L 2329, has been investigated in a series of acute experiments performed in six animal species (CHARLIER, R. *Acta Cardiol.*, Suppl. 7, 1959). A 5×10^{-7} concentration of L 2329 approximately doubled the coronary flow of the normal isolated rabbit's heart perfused under pressure (37 to 44 mm. Hg) with Locke's solution. The coronary flow was tripled by the same concentration of the drug when the heart was maintained in fibrillation by electrical stimulation. The L 2329 was able to overcome the coronary constriction which was elicited in the same fibrillating heart by posterior pituitary extracts.

The coronary flow measured with an electromagnetic rotameter in the chloralosed dog was increased after the intravenous administration of L 2329; the minimal effective dose was approximately 1 mg./kg. A dose of 10 to 20 mg./kg. appreciably improved the collateral circulation of the myocardium after ligation of the anterior descending branch of the left coronary artery; the improvement was illustrated by simultaneous changes of the electrocardiogram. The same doses did not cause any modification of the electrocardiogram in the normal unanesthetized or chloralosed animal. The vasodilator effect of L 2329 was remarkably selective for the coronary bed.

Moderate doses (10 mg./kg.) of L 2329 elicited a powerful bronchodilatation; the respiratory rate of the intact or vagotomized dog was enhanced more than the simultaneous increase in amplitude. The same doses did not completely inhibit the bronchiolar spasm that followed the systemic administration of histamine or acetylcholine. The L 2329 appeared to elicit a fairly unselective relaxation of the smooth musculature; this effect was observed on the isolated intestine, gallbladder and uterus.

Another synthetic agent has been recently proposed by Bretschneider et al. (*Arzneimittel-Forsch.*, 9: 39, 1959) as a potent and selective coronary vasodilator. It is known as 2,6-bis (diethylamino)-4,8-bispiperidino pyrimidino (5, 4-d)-pyrimidine, or RA8.

This drug appears to be more active (0.05 to 0.15 mg./per kg. administered intravenously) and longer acting (twenty to forty minutes) but it seems to have less selective effect as a coronary dilator than L 2329. The RA8, in the upper range of useful doses, elicited an appreciable dilatation of the femoral bed of the anesthetized dog; hypotension developed and was accompanied by a marked tachycardia. The blood pressure remained unchanged in the femoral vein and in the right atrium. The authors suggest that hypotension and tachycardia indicate an overdosage. These signs should be used, therefore, as a warning rather than as an end-point for the proper administration of the drug.

The RA8 appeared to be more selective than L 2329 for the vascular system, and seemed not to affect the smooth musculature of the bronchi or intestine as much. The acute toxicity in mice and the chronic toxicity in dogs appear to be similar with both substances.

The results of these studies suggest that L 2329 was a less potent, but vascularly more selective, coronary dilator than RA8. Neither agent appreciably influenced the nervous and muscular function of the heart. No information is yet available on the effects of these drugs on the cerebral and splanchnic circulations.

The biochemical properties of these agents were not reported. It should be remembered that the absorption, distribution, catabolism and excretion of a drug can limit or decide its therapeutic applications, without regard to the

value of its specific pharmacodynamic properties.

The present data were obtained in acute experiments. Therefore, the therapeutic value of prolonged administration of these drugs remains to be established. How will the patient with coronary thrombosis tolerate the hypotensive and tachycardiac effects of RA8? How will the patient with chronic angina pectoris tolerate the respiratory and intestinal effects of L 2329? Despite these questions, a new horizon seems to be opening in the treatment of coronary artery disease.

Workmen's Compensation for the Cardiac

Does Permanent Partial Disability Continue After Recovery from Myocardial Infarction

LOUIS H. SIGLER, M.D., F.A.C.C.*

Brooklyn, New York

IN THIS paper I will discuss the sixth question the Morland Commission submitted to cardiologists and internists with reference to causal relationship of strain and cardiac disability.[1] The question reads as follows: "*Suppose the case of a workman who has returned to work after recovering from a causally related myocardial infarction. He has a well healed scar and is asymptomatic. Would you consider that this workman had a permanent partial disability?*"

Three hundred seventy-two physicians answered this question. Of these, 148 or 39.6 per cent said yes, one or 0.4 per cent said probably, fifty-two or 13.9 per cent expressed the view either that there is disability from strenuous work or, its equivalent, that he is not disabled for light to moderately heavy work and 172 or 46.1 per cent said specifically no.

It would seem that before we can logically answer this question the term "asymptomatic" employed here must be carefully defined. Does this term mean that the claimant is free of symptoms only under conditions of rest or is he also free of symptoms on activity? If he presents any disturbances on activity we must know what kind of activities bring about such disturbances. If the ordinary activities to which he was accustomed before the infarction bring about disturbances he is naturally to be considered disabled. The degree of disability will depend on the extent of such activities he can carry on without disturbances. It will also depend upon the adaptability of the patient to another occupational pursuit requiring less effort.

Assuming that he can carry on the normal activities to which he was accustomed before the infarction without discomfort, we must still continue to observe the patient for a prolonged period of time to determine if the activities will result in gradual structural alterations of the heart traceable, at least partly, to the remaining damage caused by the myocardial infarction. Structural alterations that may follow in the course of time may develop stealthily and slowly, and in many cases cannot be differentiated from changes occurring in the usual course of progressive coronary atheromatosis.

POSSIBLE EFFECTS OF THE SCAR

To properly evaluate this problem we must have some understanding of what changes may take place in the heart due to the scar resulting from an infarction. This question must necessarily be answered on theoretical grounds. To my knowledge no experimental work has been carried out to determine the exact progressive damage that may occur in the rest of the heart as a result of scarification of some portion. It would seem to be relatively simple to produce areas of gross myocardial destruction in animals and observe the effects of the resulting scarification on the rest of the heart muscle and coronary vessels over a period of years, in the absence of pre-existing coronary atherosclerosis. This would give us an index of the effect of the scar *per se* on the rest of the heart.

Clinically, cardiac hypertrophy has been

* Chairman, Workmen's Compensation Committee, American College of Cardiology.

observed to develop following myocardial infarction in the absence of other disease states that may predispose to hypertrophy, such as hypertension and valvular disease. Bartels and co-workers[2] studied the autopsy protocols of forty-two patients with coronary disease and chronic infarction. In 88 per cent the weight of the heart was in excess of the average normal for the given constitutional build. The highest weight was 715 gm. In none of these was there evidence of other pathologic conditions that would cause cardiac hypertrophy. Harrison and Wood[3] observed an increase in the weight of the heart at autopsy in patients with severe coronary disease without hypertension. They thought that cardiac failure is a factor in predisposing to hypertrophy. Eyster[4] observed that stretching of the myocardium above physiologic limits results in some injury to the muscle fibers in the form of hydropic degeneration and predisposes to hypertrophy. He quoted Albrecht who believed that the stimulus to hypertrophy may be impaired nutrition of the myocardium. These authors believe that hypertrophy does not occur as a physiologic response to increased work alone but to associated pathologic changes in the myocardium.

Factors That May Cause Myocardial Failure: In scarification of the heart resulting from infarction, it may be assumed that there are at least two factors which may predispose to transient intermittant failure leading to hypertrophy. One is the stretching effects on the normal myocardial fibers during diastole caused by the unyielding fibrous tissue if the scar is tight and relatively large. Another is a greater burden on the rest of the normal myocardium by depriving a portion of the heart of its contraction, a condition caused by a large scar. In addition, some of the contractile force of the affected ventricle is spent in distending the weakened scarred portion into an aneurysmal expansion, besides propelling the main volume of blood into the aorta.

Coronary Inadequacy: Increase in the work of the normal myocardial fibers in a heart which has organized infarction calls for more blood from the coronary vessels supplying the normal heart tissue. In cases where the coronary arteries other than the occluded vessels are fairly normal, the demand for greater blood supply probably is met and the cardiac functional state may be within normal limits. In those cases where the coronary arteries generally are greatly atheromatosed and narrowed the anginal syndrome and later gross cardiac failure will ensue following the infarction. This would partly explain the differences in the reaction to the organized myocardial infarction in different patients.

Damage to Intracardiac Nerves: One fact not universally considered in the etiology of myocardial infarction is damage to the intracardiac nerves and ganglia. This may play an important role in the symptomatology of the disease and in disability. Hermann[5] observed degenerative changes in intrinsic cardiac ganglia of patients with coronary disease. How much such degeneration takes place and what effect it may have on the mechanism of cardiac activity are factors which should be investigated more fully. It is possible that such degeneration may play a part in interference with the impulse transmission and may help induce ectopic rhythms. It may also contribute to cardiac arrest and to ventricular fibrillation which often cause sudden death.

Clinical Considerations

From this short review of the possible effects of a postinfarction scar, we can readily see that no specific answer can be given in all cases as to permanence of partial disability. Each patient differs and is to be individually evaluated to properly answer this question. Furthermore, each patient must be followed up over a long period of time to determine the effect of the damage.

From clinical experience, however, we do know that many patients may carry on normal activities without discomfort for many years after a myocardial infarction. In such cases, damage to the heart caused by the infarction usually is not severe and the remaining uninvolved coronary arteries evidently have no severe atheromatosis. From a functional viewpoint these patients may therefore be considered fully recovered, with no permanent disability. Even in such cases, however, some effects of the scar may exhibit themselves in the course of time, although it would be hard to prove if such effects are not caused by progressive coronary atherosclerosis rather than the scar. There are, on the other hand, many other patients with evidence of a greater or lesser degree of cardiac impairment following an infarction which was not present before. Here we can certainly not deny that such impairment is related to the scar of infarction. These patients must be carefully scrutinized and evaluated as to the extent of disability.

SUMMARY

An attempt has been made to answer the question of whether or not permanent partial disability continues after recovery from myocardial infarction. It is postulated that the physiologicopathologic effects of the scar may result in cardiac hypertrophy due to myocardial strain and failure caused by stretching against unyielding fibrous tissue and by a greater burden on the remaining normal heart muscle. There may also be the factor of development of coronary inadequacy because of increased work of the normal portion of the myocardium. Damage to intracardiac nerves caused by scarification may be an additional factor. These factors vary greatly in different patients. It is therefore concluded that the answer to the question varies with the individual patient.

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Announcement

Members of the College are invited to submit problem cases in cardiac compensation to the Workmen's Compensation Committee for discussion. We will consider only those cases which meet the following requirements: The case history of the claimant is to be relatively short, yet thorough. It should include (1) sex, age, temperament, occupation or occupations before the attack and number of years devoted to the given occupation; (2) a bonafide description of the work or of the accident which presumably brought about the attack; (3) the time elapsing between the physical or emotional strain or trauma and the onset of symptoms of involvement of the heart; (4) the physical findings and laboratory data such as electrocardiograms, roentgenograms or other tests and (5) autopsy findings if available. Any case presenting such findings will receive preference.

After discussion and study an opinion will be forwarded to the physician who submitted the case. If the case is of general interest, the full report, discussion and opinion will be published in the JOURNAL anonymously if desired.

Inasmuch as this service will be given only for the benefit of the physician and in an attempt to advance the understanding of the compensation problems of cardiac disabilities, no case will be accepted from an insurance company or from a plaintiff's attorney, even if it is submitted by a doctor.

Communications should be submitted to my office at 255 Eastern Parkway, Brooklyn 38, New York.

LOUIS H. SIGLER, M.D., F.A.C.C., *Chairman*
Workmen's Compensation Committee
American College of Cardiology

AUTHOR INDEX VOLUME V

SUBJECT INDEX VOLUME V

(ab.) = Abstracts; (CR) = Cardiac Resuscitation; (DS) = Diagnostic Shelf; (E) = Editorial; (LE) = Letter to the Editor; (PN) = Progress Notes in Cardiology; (QC) = Query Corner; (WC) = Workmen's Compensation

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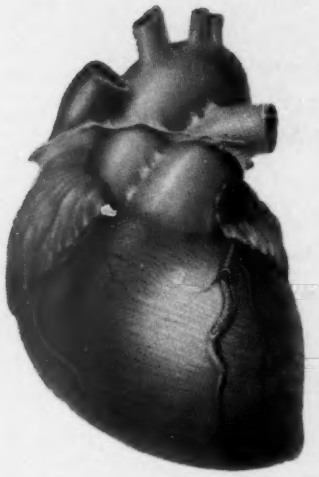

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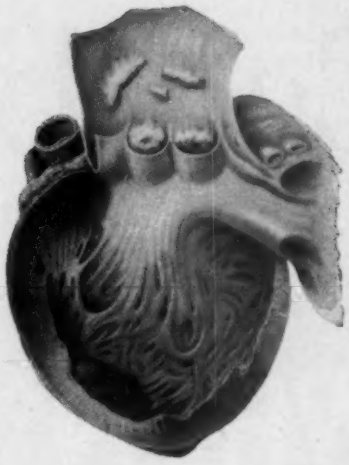

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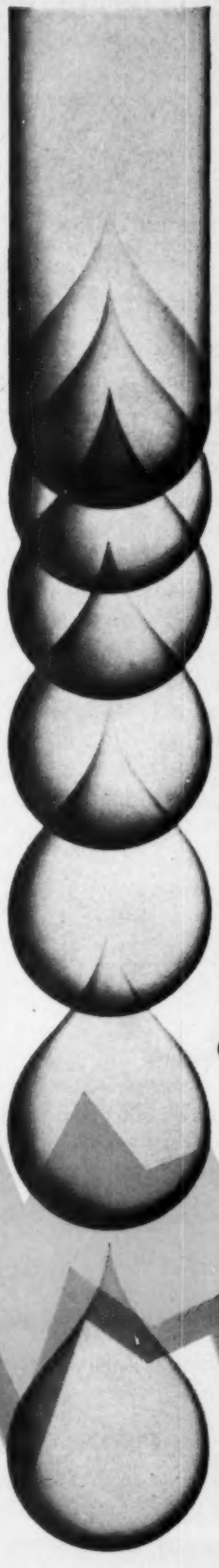

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(Abstract of the paper with above title)

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(Russek, H. I., Am. J. Med. Sc. Feb., 1960)

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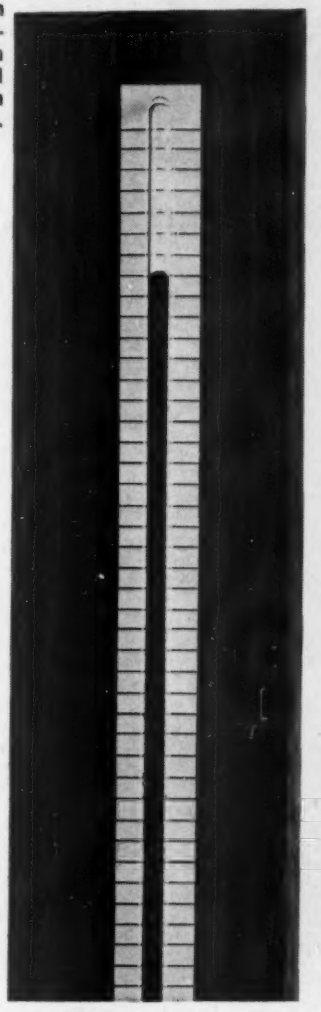

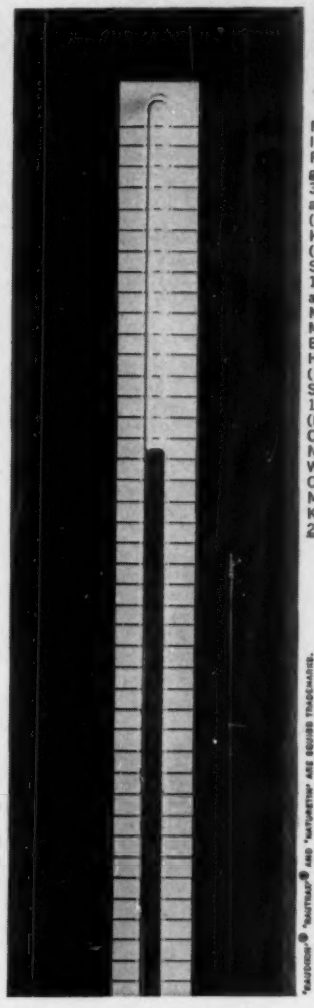

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References: 1. Reports to the Squibb Institute, 1960. 2. David, N. A.; Porter, G. A., and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 3. Stenberg, E. S., Jr.; Benedetti, A., and Forsham, P. H.: Op. cit. 5:46 (Feb.) 1960. 4. Fuchs, M.; Moyer, J. H., and Newman, B. E.: Op. cit. 5:55 (Feb.) 1960. 5. Marriott, H. J. L., and Schamroth, L.: Op. cit. 5:14 (Feb.) 1960. 6. Ira, G. H., Jr.; Shaw, D. M., and Bogdonoff, M. D.: North Carolina M. J. 21:19 (Jan.) 1960. 7. Cohen, B. M.: M. Times, to be published. 8. Breneman, G. M. and Keyes, J. W.: Henry Ford Hosp. M. Bull. 7:281 (Dec.) 1959. 9. Forsham, P. H.: Squibb Clin. Res. Notes 2:5 (Dec.) 1959. 10. Larson, E.: Op. cit. 2:10 (Dec.) 1959. 11. Kirkendall, W. M.: Op. cit. 2:11 (Dec.) 1959. 12. Yu, P. N.: Op. cit. 2:12 (Dec.) 1959. 13. Weiss, S.; Weiss, J., and Weiss, B.: Op. cit. 2:13 (Dec.) 1959. 14. Moser, M.: Op. cit. 2:13 (Dec.) 1959. 15. Kahn, A., and Grenblatt, I. J.: Op. cit. 2:15 (Dec.) 1959. 16. Groliman, A.: Monographs on Therapy 5:1 (Feb.) 1960.

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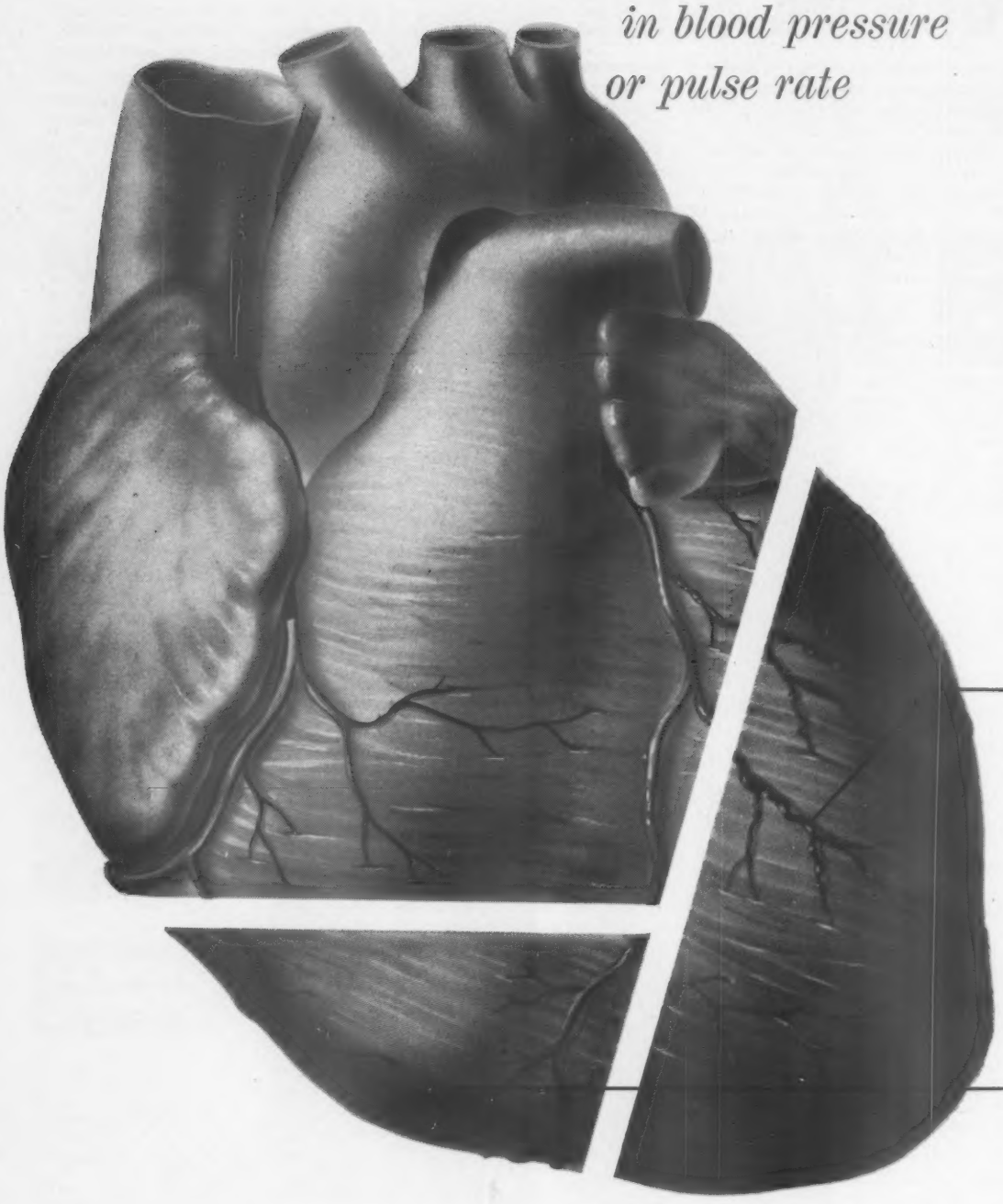
improve coronary blood flow with no significant change in blood pressure or pulse rate



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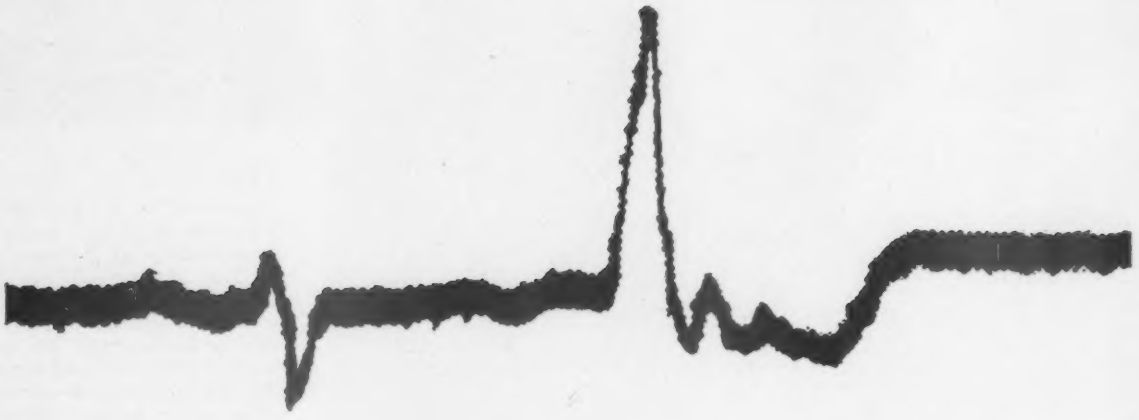

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References: 1. Zapata-Diaz, J., et al.: Am. Heart J. 43:854, 1952. 2. Modell, W.: In Drugs of Choice, C.V. Mosby Co., St. Louis, 1958, p. 454. 3. Kayden, H. J., et al.: Mod. Concepts Cardiovasc. Dis. 20:100. 1951. 4. Miller, H., et al.: J.A.M.A. 146:1004, 1951.

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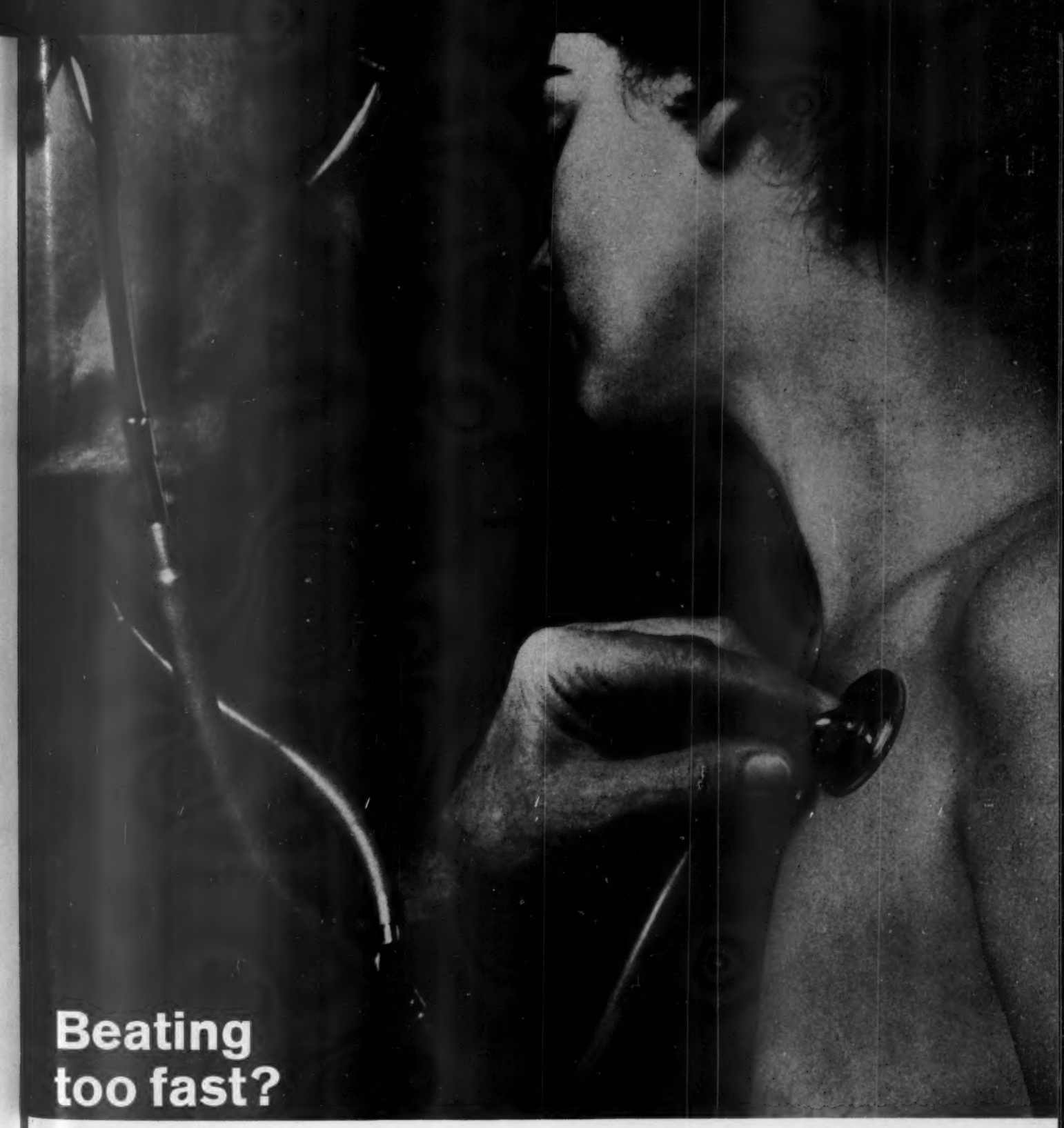

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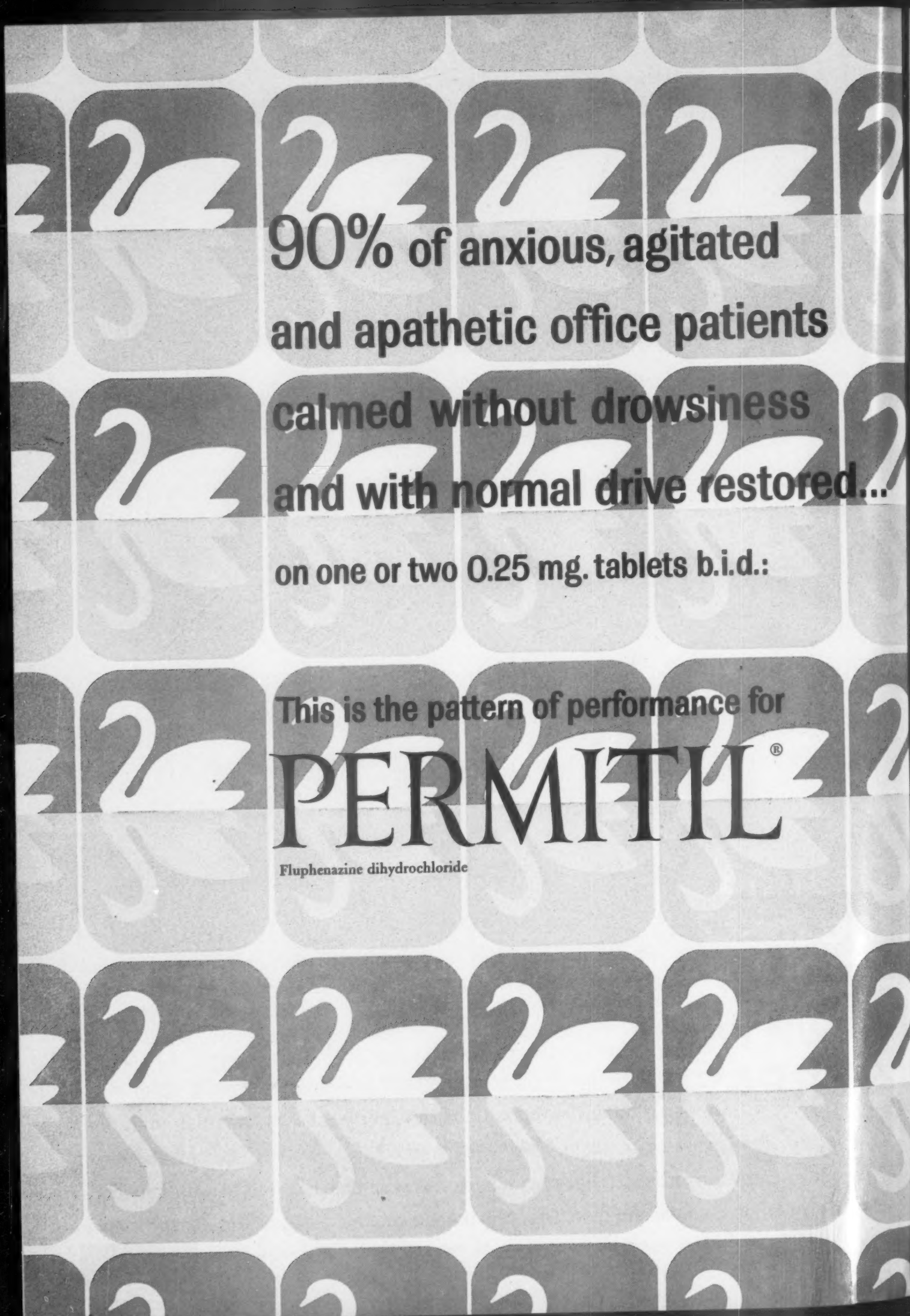
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REFERENCES: 1. Ayd, F. J., Jr.: Current Therapeutic Research 1:41 (Oct.) 1959. 2. Recent compilation of case reports received by the Medical Department, White Laboratories, Inc.

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exclusive oral
Sustained Medication*
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QUINAGLUTE DURA-TAB S.M. tablets maintain effective uniform blood levels around the clock, day and night.

better tolerated
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Bottles of 30, 100 and 250.

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1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957.
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4. Bellet, S.: Amer. J. Cardiology 4:268, 1959.

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A. Because corn oil is a polyunsaturated vegetable oil that is clinically effective in reducing cholesterol levels

Effect of Dietary Fat

A wide variety of diet plans have been used – carefully controlled liquid formulas as the sole food, selected fats added to a low-fat basal diet, or "normal diets" in which the only change has been in the selection of foods so that the ratio of polyunsaturated to saturated fats is increased. In general, diets rich in polyunsaturated fatty acids have appeared to be more effective in lowering serum cholesterol levels than are low-fat (high carbohydrate) diets. The ratio of polyunsaturated to saturated fatty acids seems to be one of the determining factors: the cholesterol level is lower when a polyunsaturated vegetable oil is the predominant fat in the diet.

SELECTED BIBLIOGRAPHY: Ahrens, E. H., Jr., J. Hirsch, W. Insull, Jr., T. T. Tsaltas, R. Bloomstrand, and M. L. Peterson, J. Am. Med. Assoc. *164*, 1950-11 (1957). Beveridge, J. M. R., Am. J. Public Health *47*, 1370-80 (1957). Keys, A., J. T. Anderson, and F. Grande, Circulation *19*, 201-14 (1959). Kinsell, L. W., G. D. Michaels, and J. P. Dailey, Circulation *16*, 479-80 (1957). Malmros, H., and G. Wigand, Lancet *273*, 1-8 (1957).

Suggestions for Practical Diets

Research on the relationship of dietary fats to human serum cholesterol values has led to the conclusion that the effect must be ascribed to a change in the nature of the dietary fat – in particular, to a change in the ratio of polyunsaturated to saturated fats. Data so far reported support the hypothesis that there is an optimum ratio of polyunsaturated to saturated fats in diets for cholesterol control.

SELECTED BIBLIOGRAPHY: Kinsell, L. W., G. D. Michaels, R. W. Friskey, and S. Splitter, Lancet *274*, 334-9 (1958). Ahrens, E. H., Jr., J. Hirsch, M. L. Paterson, W. Stoffel, and J. W. Farquhar, J. Am. Med. Assoc. *170*, 2198-9 (1959). Keys, A., J. T. Andrews, and F. Grande, Circulation *19*, 201-14 (1959).

How Mazola® Corn Oil May Help in Dietary Control of Hypercholesterolemia

Sensible precautions recommended by many leading medical authorities are: 1) control of total caloric intake to avoid obesity, 2) limitation of total fat intake to about ⅓ of the total calories, and 3) selection of foods such that about ⅓ to ½ of the fat be polyunsaturated. In the simplest terms, these suggestions mean use of a polyunsaturated vegetable oil such as Mazola Pure Corn Oil in place of more saturated cooking fats.

Mazola Corn Oil has a uniformly high linoleate content and a ratio of linoleate to saturates which is consistently higher than in other commonly available edible oils. Thus, where dietary control of serum cholesterol is indicated, Mazola Corn Oil is second to none among the leading oils in

recommend corn oil for of serum cholesterol?

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MAZOLA Corn Oil has the following average composition

Glycerides of Fatty Acids	% by weight	Grams/ tablespoon
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Linoleates	54 (52-56)	7
Saturates, Total	11 (9-12)	1.4
Natural Sitosterols	1 (0.9-1.3)	0.14
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Cholesterol	None	None
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Calories.		125

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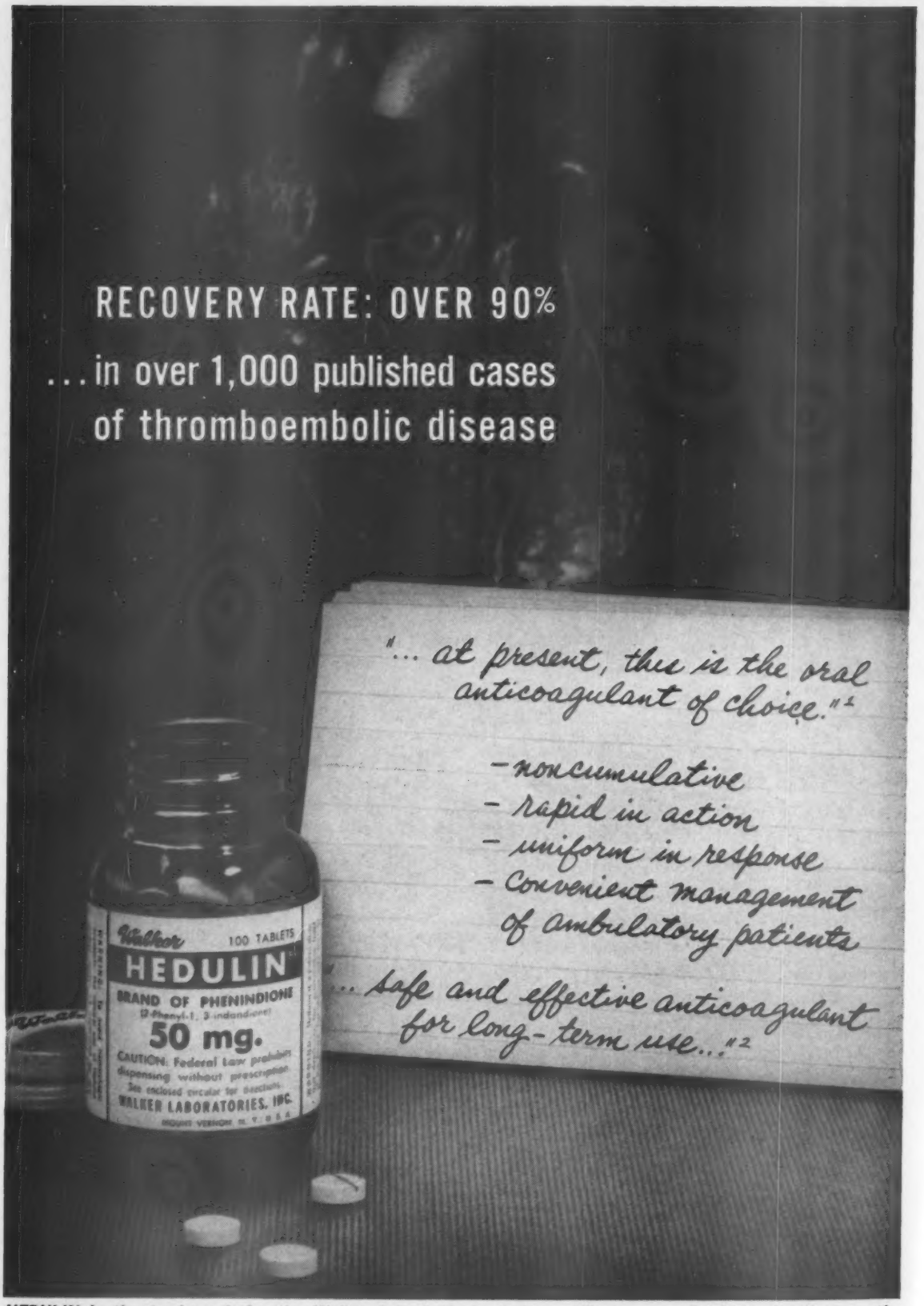

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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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1. Feinblatt, T. M., and Ferguson, E. A.: New Eng. J. Med. 256:331 (Feb.) 1957.
2. Kupersmith, I. H.: International Record of Medicine, Vol. 171 No. 10 (Oct.) 1958.
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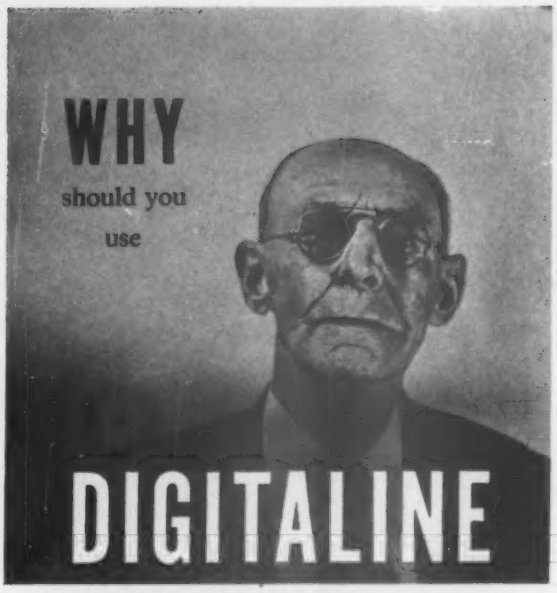

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New Tenuate produces a pure anorexic effect, free of CNS stimulation.[1] EKG studies[2] prove Tenuate does not affect heart rate, blood pressure, pulse or respiration.

Tenuate produces a satisfactory, progressive weight loss, often with minimum reliance on strict dieting or calorie counting.[1]

Dosage: *One 25 mg. tablet one hour before meals. To control nighttime hunger, an additional Tenuate tablet in mid-evening will not induce insomnia.*

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1. Spielman, A.D.: Mich. Acad. Gen. Prac. Symposium, Detroit, 1959.
2. Alfaro, R. D. and Gracanin, V.: *to be published.*

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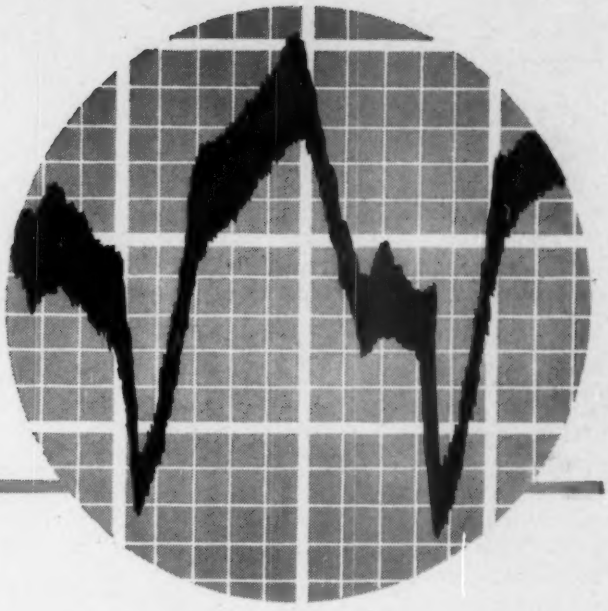

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ADMINISTRATION: Intramuscularly, or if necessary, intravenously.

SUPPLIED: Quinidine Hydrochloride Injectable (0.6 gm.) in 5 cc. ampuls. Quinidine Hydrochloride Injectable (0.18 gm.) in 1½ cc. ampuls. Also available for oral administration—Quindul (Quinidine Sulfate, Brewer) (3 gr.) in capsules, tablets and enteric coated tablets.

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1. Armbrust, C.A., Jr., and Levine, S.A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases. Circulation 1:28 (1950)
2. Bell, G.D., Bradley, R.B., and Hurxthal, L.M.: Paroxysmal Tachycardia, Experiences with Massive Doses of Quinidine Intravenously in a Refractory Case. Circulation 1:939 (1950)

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safe and practical treatment of the postcoronary patient

A basic characteristic of the postcoronary patient, whether or not cholesterol levels are elevated, is his inability to clear fat from his blood stream as rapidly as the normal subject.[1-3] *Figure #1* graphically illustrates this difference in fat-clearing time by comparing atherosclerotic and normal subjects after a fat meal.[3]

"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in *figure #2,* the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,[4] and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.[5]

In *figure #3,* the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

'Clarin', which is heparin in the form of a *sublingual tablet,* has been demonstrated to clear lipemic serum.[2,6,7] Furthermore, a two-year study using matched controls resulted in a statistically significant reduction of recurrent myocardial infarction in 130 patients treated with 'Clarin'.[8]

'Clarin' therapy is simple and safe, requiring no clotting-time or prothrombin determinations. Complete literature is available to physicians upon request.

References: 1. Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. 2. Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. *7*:225 (Apr.) 1959. 3. Stutman, L. J., and George, M.: Clin. Res. *7*:225 (Apr.) 1959. 4. Wilkinson, C. F., Jr.: Annals of Int. Med. *45*:674 (Oct.) 1956. 5. Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. *163*:727 (March 2) 1957. 6. Fuller, H. L.: Angiology *9*:311 (Oct.) 1958. 7. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959. 8. Fuller, H. L.: Circulation *20*:699 (Oct.) 1959.

Clarin*

(sublingual heparin potassium, Leeming)

Fig. 1

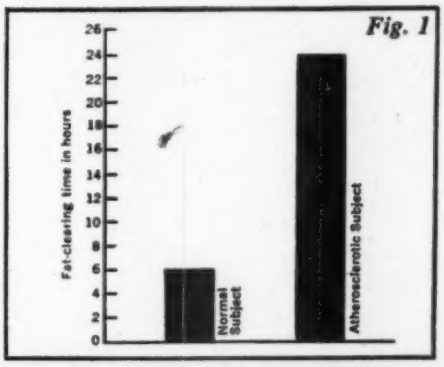


Fig. 2

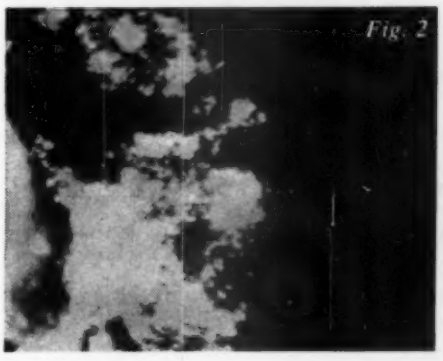
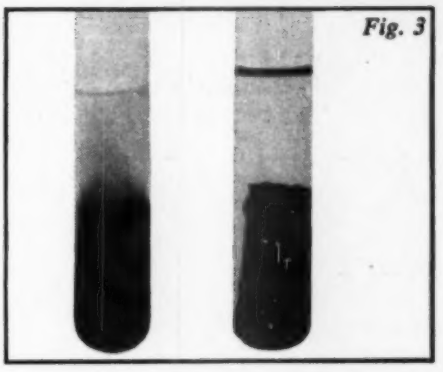


Fig. 3



Indication: For the management of hyperlipemia associated with atherosclerosis, especially in the postcoronary patient.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

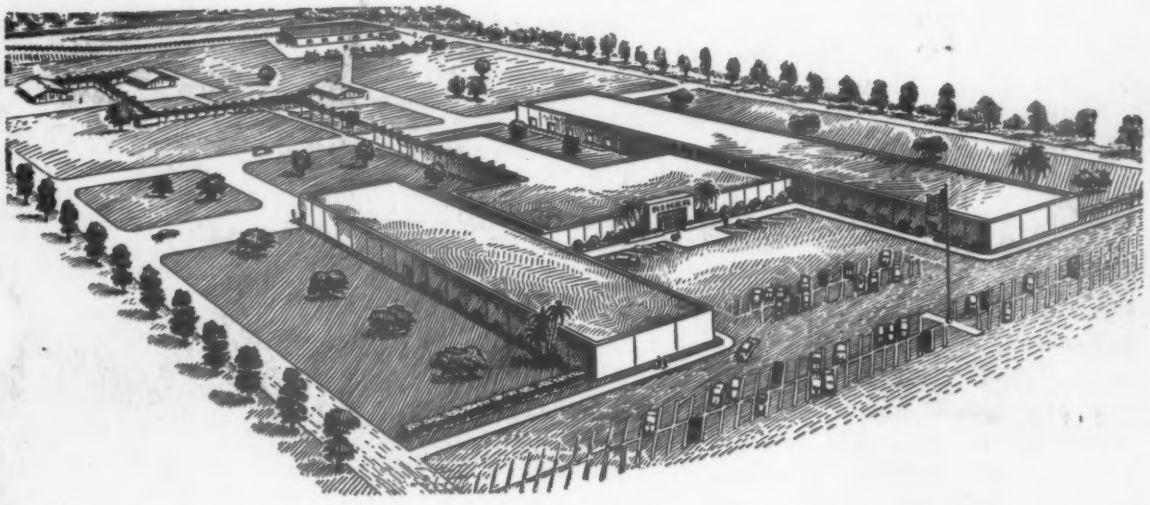
Supplied: 'Clarin' is supplied in bottles of 50 pink, sublingual tablets, each containing 1500 I.U. of heparin potassium.

*Registered trade mark. Patent applied for.

Thos. Leeming & Co., Inc.
New York 17, N. Y.

Service to the Profession

Riker Laboratories is proud to announce that Darwin Laboratories has become its newest family member. The expanding Riker facilities now include research devoted to heparin therapy as part of its service to the medical profession.



lipo-hepin®

Heparin Sodium U.S.P., aqueous

Dual Protective Action

1. Reliable anticoagulation with 1 or 2 injections daily.
2. Rapid lipid-clearing action.

Riker Northridge, California